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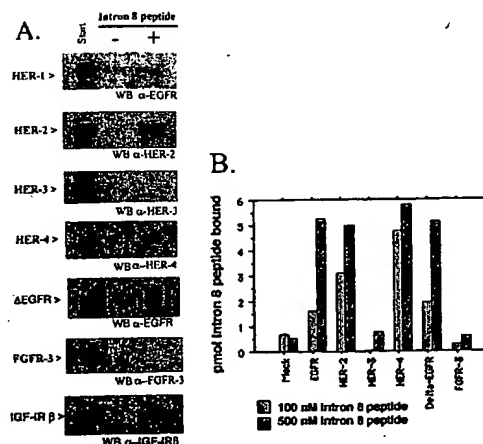
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(54) Title: COMPOSITIONS AND METHODS FOR MODULATING SIGNALING MEDIATED BY IGF-1 RECEPTOR AND ERBB RECEPTORS



(57) Abstract: The binding interactions between herstatin, or the intron 8-encoded receptor binding domain (RBD Int8) thereof, and several receptors were analyzed. According to aspects of the present invention, herstatin and the intron 8-encoded domain bind with high affinity (e.g., nM concentrations) to all four of the ErbB receptors: EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); and HER-4 (erbB-4), as well as to ΔEGFR and the IGF-1 receptor, and such binding has utility to modulate signaling mediated by these receptors. Herstatin inhibited target receptor-mediated activation of intracellular signaling pathways (e.g., PI3/Akt, IRS-2, etc., pathways) that are important in cell survival, and further inhibited target receptor-mediated (e.g., IGF-1/IGF-1R-mediated) survival of cancer cells. Aspects of the present invention thus provide methods and compositions for the treatment of cancer, including cancer refractory to other erbB-based agents, and of other conditions and disorders characterized by target receptor expression, over-expression, signaling, and/or aberrant signaling. Additional aspects provide methods of targeted drug delivery.



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# COMPOSITIONS AND METHODS FOR MODULATING SIGNALING MEDIATED BY IGF-1 RECEPTOR AND ERBB RECEPTORS

## FIELD OF THE INVENTION

5 This invention relates generally to signaling through IGF-1 receptors and through ErbB family member receptors, and more specifically to novel methods and compositions for modulating intracellular signaling mediated by IGF-1 receptor and by ErbB family receptors, for cell targeting, and for the treatment of cancer and other target receptor-mediated conditions and disorders.

## CROSS-REFERENCE TO RELATED APPLICATIONS

10 This application claims the benefit of priority to United States Provisional Patent Application Serial Number 60/590,473, filed 23 July 2004, and entitled COMPOSITIONS AND METHODS FOR TREATING CANCER BY MODULATING IGF-1 RECEPTOR AND ERBB  
15 RECEPTORS, to United States Provisional Patent Application Serial Number 60/564,893, filed 22 April 2004, of same title, both of which are incorporated by reference herein in their entirety.

## STATEMENT REGARDING FEDERALLY-SPONSORED RESEARCH

20 This work was partially funded by NIH grant number CA83503, and the United States government has, therefore, certain rights to the present invention.

## BACKGROUND

25 The ErbB receptor family consists of four receptor tyrosine kinases: EGFR (HER-1, erbB-1), HER-2 (erbB-2), HER-3 (erbB-3) and HER-4 (erbB-4). Aberrant expression of ErbB receptors by mutational activation, receptor overexpression, and tumor production of ligands contributes to the development and maintenance of a variety of human cancers (*e.g.*, Olayioye et al., *Embo J.*, 19:3159-67, 2000).

30 The ErbB receptors, with one exception, are activated by several ligands with an EGF core domain (EGF-related growth factors). HER-2 receptor, the exception, is recruited as a preferred dimer partner with other ligand-binding erbB receptors (*Id*). The eleven mammalian

EGF-like ligands are all agonists, whereas *Drosophila* has the ligand 'Argos' that inhibits activation of the EGFR (Dougall et al., *Oncogene* 9:2109-23, 1994; Hynes & Stern, *Biochim. Biophys. Acta* 1198:165-84, 1994; Tzahar & Yarden, *Biochim. Biophys. Acta* 1377:25-37, 1998).

Although the HER-2 receptor does not directly bind EGF-like ligands, a secreted product of an HER-2 alternative transcript, herstatin, binds with high affinity ( $K_D \approx 14$  nM) to the ectodomains of HER-2 and the EGF receptor (EGFR). Herstatin consists of a segment of the HER-2 ectodomain (340 amino acids that are identical to the N-terminal subdomains I and II), followed by 79 amino acids encoded by intron 8 of the HER-2 gene that function as a receptor binding domain (RBD) (Doherty et al., *Proc. Natl. Acad. Sci. USA* 96:10869-74, 1999).

Herstatin blocks homomeric and heteromeric ErbB receptor interactions, inhibits activation of the PI3K/Akt pathway initiated by EGF, TGF $\alpha$ , and Heregulin, causes growth arrest, and has substantial utility as an anti-cancer agent (*Id.* and see, e.g., Azios et al., *Oncogene* 20:5199-209, 2001; Jhabvala-Romero et al., *Oncogene* 22:8178-86, 2003; and Justman & Clinton, *J. Biol. Chem.* 277:20618-24, 2002).

Anti-erbB receptor antibody agents, such as the HER-2-specific antibody rhuMAb4D5 (HERCEPTIN<sup>TM</sup>) have been approved for cancer therapy. Significantly, however, tumor cells may be inherently resistant, or gain resistance, to anti-erbB receptor therapies through activation of IGF-IR pathways (see, e.g., Chakravarti et al., *Cancer Res.* 62:200-7, 2002 (discussing IGF-1R-mediated resistance to AG1478, an EGFR tyrosine kinase inhibitor); Lu et al., *J. Biol. Chem.* 279:2856-65, 2004; Lu et al., *J. Natl. Cancer Inst.*, 93:1852-7, 2001 (discussing IGF-1R-mediated resistance to Herceptin<sup>TM</sup>, in the context of breast cancer); and Camp, 2005 (discussing IGF-1R-mediated resistance to Iressa, a small molecule EGFR inhibitor, in the context of breast and prostate cancer)). Activation of the IGF-I receptor (IGF-IR) by IGF-I promotes, *inter alia*, proliferation, survival, transformation, metastasis, and angiogenesis (see, e.g., Baserga, *Hum. Pathol.* 31:275-6, 2000; and Wang & Sun, *Curr. Cancer Drug Targets* 2:191-207, 2002), and signaling through both IGF-IR and EGF receptors is central to tumorigenesis.

There is, therefore, a pronounced need in the art not only to further investigate and characterize the interactions among the erbB family receptors, but to identify modulators of the signaling mediated by erbB receptors and IGF-1 receptors. There is a need in the art for a multi-



functional inhibitor that *simultaneously* targets both the EGF and IGF-IR families. There is a pronounced need in the art to identify and develop modulators (*e.g.*, inhibitors) of erbB receptors and of IGF-IR modulators as therapeutic agents (*e.g.*, anti cancer agents). There is a need in the art to further assess the receptor-modulating utilities of herstatin and its intron 8-encoded RBD.

5

## SUMMARY OF THE INVENTION

According to particular aspects of the present invention, herstatin, and the intron 8-encoded domain thereof (referred to herein as "int8 RBD"), bind with high affinity (*e.g.*, at nM concentrations) to: all four of the ErbB receptors EGFR (HER-1, erbB-1), HER-2 (erbB-2),  
10 HER-3 (erbB-3), and HER-4 (erbB-4); as well as to  $\Delta$ EGFR and the IGF-1 receptor. Moreover, such target receptor binding has been shown and disclosed herein to have novel and substantial utility to modulate intracellular signaling mediated by these receptors.

Particular embodiments provide novel methods and compositions for the treatment of cancer and other conditions and disorders characterized by target receptor expression or over-  
15 expression, and/or target receptor mediated signaling or aberrant signaling.

Specific embodiments provide a method for treating cancer, comprising administering a therapeutically effective amount of herstatin, or of a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, wherein the cancer cells express  
20 at least one of the target receptors. Alternatively, a therapeutically effective amount of a Int8 RBD polypeptide, or of a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, is administered. The methods also encompass treatments where the cancer cells further express EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

25 Further embodiments provide combination therapies, further comprising, administration of a therapeutically effective amount of: a receptor-specific antibody that binds to the extracellular domain of a target receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), and IGF-1R; or of a chemotherapeutic (*e.g.*, anti-neoplastic) agent.

Additional embodiments provide pharmaceutical compositions for treating cancer and other conditions and disorders characterized by target receptor expression or over-expression, and/or target receptor-mediated signaling or aberrant signaling, comprising, along with a pharmaceutically acceptable diluent, carrier or excipient, herstatin, or a variant thereof, that  
5 binds to the extracellular domain of a target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4); IGF-1R and combinations thereof, wherein the cancer cells express at least one of the target receptors. Alternatively, the inventive compositions comprise, along with a pharmaceutically acceptable diluent, carrier or excipient, a  
10 Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, wherein the cancer cells express at least one of the target receptors.

The compositions also have substantial utility in treatments where the target cells (*e.g.*, cancer cells) further express EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

15 Additional aspects provide novel methods of targeted drug delivery.

Specific embodiments provide methods for targeting a therapeutic agent to cancer cells, comprising attaching the therapeutic agent to herstatin, or to a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4); IGF-1R and combinations thereof, wherein the cancer cells express  
20 at least one of the target receptors. Alternatively, the therapeutic agent is attached to a Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4); IGF-r and combinations thereof, wherein the cancer cells express at least one of the target receptors.

The targeting methods encompass treatments wherein the cancer cells further express  
25 EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

Preferably, for the above-described methods and compositions, the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present. Preferably, the herstatin, or variant thereof,

further comprises at least one N-linked glycosylation site, and binds to the extracellular domain of EGF receptor with an affinity binding constant of at least about  $10^7 \text{ M}^{-1}$ , or of at least about  $10^8 \text{ M}^{-1}$ .

Preferably, for the above-described methods and compositions, the Int8 RBD polypeptide, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length. Preferably, the Int8 RBD polypeptide, or variant thereof binds to the extracellular domain of target receptor with an affinity binding constant of at least about  $10^7 \text{ M}^{-1}$ , or of at least about  $10^8 \text{ M}^{-1}$ .

Additional embodiments provide for a novel form of HER-3 (SEQ ID NO:14) that does not bind to herstatin or to Int8 RBD polypeptides, thus providing screening assays for cells having impaired responsiveness to herstatin or int8 RBD polypeptides.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A demonstrates that the RBD Int8 polypeptide, purified from bacteria and immobilized on Protein S Sepharose™ 'pulled down' IGF-IR from 3T3 cell extracts.

Figure 1B illustrates a binding curve showing saturable binding by the RBD Int8 polypeptide that is specific for IGF-IR.

Figure 1C illustrates the results of ELISA assays showing that herstatin, purified from transfected S2 insect cells, exhibited dose-dependent binding to IGF-1R at nM concentrations.

Figure 1D illustrates binding curves showing that full-length herstatin exhibited saturation binding to IGF-IR 3T3 cells, demonstrating nM binding affinity.

Figures 2A and 2B show that herstatin prevented activation of IGF-1R by IGF-1 in MCF-7 cells. Figure 2A shows a representative Western immunoblot of IGF-IR immunoprecipitation of IGF-I-treated MCF-7 and MCF-7/Hst cell lysates. Figure 2B shows a graphical representation of two independent experiments of IGF-I-induced activation of the IGF-I receptor. The lower portion of Figure 2A shows that herstatin not only prevented activation of IGF-1R by IGF-1 in MCF-7 cells, but also caused down-regulation of IGF-1R.

Figure 3A shows, using 'pull-down' assays, that the herstatin RBD Int8 polypeptide

bound in a specific manner to EGFR, HER-2, HER-4, IGF-1R and  $\Delta$ EGFR, but did not bind to a mutant form of HER-3, to FGFR-3, or to mock-transfected cells.

Figure 3B shows, using ELISA, that the Int8 polypeptide bound in a specific and dose-dependent manner to EGFR, HER-2, HER-4, and  $\Delta$ EGFR, but not to a mutant form of HER-3, FGFR-3, or mock-transfected cells.

Figures 4A and 4B illustrate Western blot analyses of RBD Int8 polypeptide binding to different forms of HER-3: Figure 4A shows lack of RBD Int8 polypeptide binding to a form of HER-3 having a single point mutation resulting in substitution of Glu for Gly in the ectodomain of HER-3 (Accession #: NM\_001982, nucleotide # 1877, and amino acid residue # 560).

Figure 4B shows high-affinity binding by Int8 RBD polypeptide to endogenous HER-3 on MCF7 breast cancer cells, independent of ligand activation.

Figure 4C shows binding of the Int8 RBD polypeptide to purified (wild-type) HER-3.

Figure 5A illustrates a binding curve showing that the Int8 RBD polypeptide bound to HER-2-transfected Cos-7 cells ( $K_D = 50 \pm 6$  nM; open squares) and to EGFR-transfected Cos-7 cells ( $K_D = 78 \pm 10$  nM; filled squares) with binding affinities, assessed by comparative nonlinear regression analysis, that were not significantly different ( $P = 0.40$ ).

Figure 5B illustrates a binding curve showing that the Int8 RBD polypeptide bound to the IGF-IR/3T3 cells with an affinity ( $K_D = 70 \pm 21$ ) that was not significantly different ( $P = 0.96$ ) from the affinity for HER-2/3T3 cells ( $K_D = 66 \pm 16$ ).

Figure 6A illustrates binding curves showing a direct comparison of the binding of herstatin to 3T3/HER-2 and 3T3/IGF-IR cells.

Figure 6B illustrates Cos-7 cell herstatin binding curves showing that the dissociation constant of herstatin for EGFR was similar to that of HER-2, and was unaffected by ligand occupation.

Figure 6C is a saturation binding curve showing that herstatin exhibited saturation binding to endogenous receptors in A431 epidermoid carcinoma cells, which express very high levels of EGFR and low levels of other ErbB receptors.

Figures 7A and 7B show that while herstatin blocked intracellular signaling (MAPK phosphorylation) by Heregulin (the ligand for HER-3 and HER-4) in MCF-7 cells (FIGURE 7A,

right-most two time series in upper panel), it does not affect FGF signaling (MAPK phosphorylation) in MCF-7 cells (FIGURE 7A, right-most two time series in lower panel), and did not inhibit IGF-1-mediated ERK phosphorylation in MCF-7 cells (FIGURE 7B).

Figure 7C shows that herstatin down-regulates HER-1, HER-3 and HER-4 receptors in MCF-7 cells.

Figure 7D shows that herstatin blocks EGF/EGFR-mediated intracellular signaling (MAPK phosphorylation) in MCF-7 cells.

Figure 8A and 8B show that herstatin inhibited IGF-1/IGF-1R-mediated activation of the PI3/Akt pathway that is important in cell survival. Figure 8A shows representative Western immunoblot showing IGF-I-induced Akt/PKB activation in MCF7 and MCF7/Hst cells. Figure 8B shows the graphical representation of 3 separate experiments, according to Figure 8A.

Figure 9 shows the effect of herstatin -expression on the expression levels of various signaling proteins. Herstatin expression in MCF7 breast carcinoma cells down-regulated IGF-1R, IRS-1, IRS-2 (also important in cell survival), and pKB/Akt expression, but MAPK expression was unaffected. Herstatin expression also induced expression of the p66 isoform of Shc, which is not detectable by Western Blot in parental MCF7 cells.

Figures 10A and 10B show the effect of herstatin on IGF-I-stimulated cell proliferation. Herstatin expression blocked IGF-1-mediated survival of MCF7 cells. Growth of parental MCF7 breast carcinoma cells and MCF7 cells stably transfected with herstatin, (A) low hst-expressing clone, and (B) high hst-expressing clone, was determined by the MTS assay as described under Example 1 herein. Cells were serum-starved for 24 hours and then treated with 5nM IGF-1 or vehicle, and growth was assessed at the indicated days.

## DETAILED DESCRIPTION OF THE INVENTION

Herstatin is the only known alternative receptor product that functions as a ligand, and is the only mammalian secreted ligand that inhibits members (HER-2 and EGFR) of the EGF receptor family (see, e.g., for background: Dougall et al., *Oncogene* 9:2109-23, 1994; Hynes & Stern, *Biochim Biophys Acta* 1198:165-84, 1994; and Tzahar & Yarden, *Biochim Biophys Acta* 1377:M25-37, 1998).

Aspects of the present invention describe and support HER-3,  $\Delta$ EGFR, HER-4, and the IGF-IR as four additional (in addition to the previously disclosed binding to EGFR and HER-2) novel targets of herstatin and/or of its intron 8-encoded receptor binding domain (herein referred to as "Int8 RBD" or "RBD int8" polypeptide).

5 Additional aspects describe and support applicant's determination that intron 8 of the HER-2 gene, which is retained in an alternative HER-2 transcript (that encodes herstatin, encodes a 79-amino acid receptor binding domain (RBD) polypeptide (RBD Int8 polypeptide) that specifically binds to EGFR, HER-2, HER-3,  $\Delta$ EGFR, HER-4, and the IGF-IR (RBD Int8 target receptors) with high affinity (*e.g.*, nM affinity), but not to a mutant form of HER-3 having  
10 a substitution of Glu for Gly in the ectodomain of HER-3 at residue number 560, nor to the FGFR-3.

In particular aspects, as disclosed herein, herstatin inhibits target receptor-mediated activation of the intracellular signaling pathways (*e.g.*, PI3/Akt, IRS-2, etc., pathways) that are important in cell survival, and further inhibit target receptor-mediated survival of cancer cells.  
15 Therefore, herstatin and/or RBD Int8 polypeptides and herstatin-, and/or RBD Int8 polypeptide-based agents (*e.g.*, conjugates with toxins, radionuclides, etc.) have utility as therapeutic agents for treatment of diseases or conditions (*e.g.*, cancer) characterized by cellular expression, or over-expression of a target receptor (*e.g.*, of EGFR, HER-2, HER-3,  $\Delta$ EGFR, HER-4, and/or the IGF-IR).

20 According to additional aspects, while the intron 8-encoded domain was demonstrated herein to be critical for receptor binding, it did not affect target receptor activity indicating that the N-terminal subdomains I and II of herstatin are likely required for receptor inhibition.

Furthermore, as disclosed herein, while the intron 8-encoded RBD appears to be critical for the receptor binding activity of herstatin, it is not conserved between humans and rats,  
25 despite a high degree of sequence identify between the HER-2 receptor and its rat ortholog, neu. Consistent with this result, there are distinct regions in the ectodomains of these two receptors that have very little identity (Stein and Staros, 2000).

According to particular aspects, therefore, the HER-3, HER-4 and  $\Delta$ EGF receptors are specific targets of herstatin and/or the RBD Int8 polypeptide, likely based on specific binding of

the RBD Int8-encoded domain. Moreover, and as in the case of the structurally related EGFR and HER-2 receptors, herstatin binds to and blocks the dimerization of the HER-3, HER-4 and  $\Delta$ EGF receptors. As shown herein, for example, herstatin inhibits HER-4-mediated activation of the PI3/Akt pathway important in cells survival.

5 HER-3 is unique in the erbB family in that it is kinase-deficient, requiring an active receptor partner to signal. Additional aspects provide a mutant form of HER-3 that shows a lack of herstatin and/or RBD Int8 polypeptide binding. This mutant or variant form, therefore, has utility according to particular aspects of the present invention, for identification and/or screening of cells that are, at least to some extent, non-responsive, or at least less responsive to herstatin  
10 and/or RBD Int8 polypeptides, compared to cells expressing HER-3 forms that do bind herstatin and/or RBD Int8 polypeptides.

Surprisingly, according to particular aspects of the present invention, the IGF-1 receptor (IGF-1R) is also a specific target of herstatin and/or the RBD Int8 polypeptide, based on specific binding of the RBD Int8-encoded domain. The binding of herstatin and/or the RBD Int8  
15 polypeptide to the IGF-1R with high affinity (*e.g.*, nM affinity) was entirely unexpected, because receptor ligands do not typically cross-react with receptors from different families. Consistent with this result, however, the IGF-1R appears to have regions of ectodomain sequence homology with the EGFR, and it is known that "crosstalk" occurs between the families, most notably, 'transactivation' of the EGFR by IGF-1 (Ahmed T, Farnie N, et al., 2004; and references  
20 therein). Therefore, herstatin and/or RBD Int8 polypeptides and herstatin-, and/or RBD Int8 polypeptide-based agents (*e.g.*, conjugates with toxins, radionuclides, etc.) have utility as therapeutic agents for treatment of diseases or conditions (*e.g.*, cancer) characterized by cellular expression, or over-expression of the IGF-1R.

In particular determinations, the binding affinity of herstatin, but not of the RBD Int8  
25 polypeptide, was found to be somewhat weaker for IGF-1R than for HER-2 or the EGFR, indicating less stabilizing interaction between the N-terminus of herstatin and the IGF-1 receptor ectodomain relative to the corresponding EGFR ectodomain regions (the IGF-1R does not have a homologous dimerization loop (Garrett et al., *Cell* 110:763-73, 2002).

According to additional aspects of the present invention, herstatin, the RBD Int8

polypeptide and herstatin- and/or RBD Int8 polypeptide-based agents can be used to target EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR, and/or modulate signaling mediated by these target receptors.

## 5 DEFINITIONS

“Herstatin” refers to the polypeptides of SEQ ID NO:2, and additionally includes functional (*e.g.*, target receptor-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins, derivatives and fusion proteins thereof.

10 “RBD Int8 polypeptide” refers to the polypeptides of SEQ ID NO:1, and additionally includes functional (*e.g.*, target receptor-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins, derivatives and fusion proteins thereof.

“Mutant RBD Int8 polypeptide” or “mutant Int8 RBD polypeptide” refers to the intron 8-encoded receptor binding domain variants (with an Arg to Ile mutation at residue 31 thereof) of 15 SEQ ID NO:3), and additionally includes functional (*e.g.*, target receptor non-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins, derivatives and fusion proteins thereof. Representative, corresponding herstatin variants (Arg to Ile mutation at residue 371) are given as SEQ ID NO:4.

Functional herstatin, functional herstatin variants, functional Int8 RBD polypeptides, and 20 functional Int8 RBD polypeptide variants are those proteins that display one or more of the biological activities of herstatin, including but not limited to target receptor binding, inhibition of receptor dimerization, modulation of receptor-mediated signal transduction, modulation of receptor activation, receptor down-regulation, etc. Particular aspects provide Functional herstatin, functional herstatin variants, functional Int8 RBD polypeptides, and functional Int8 25 RBD polypeptide variants having various binding affinities, including but not limited to those having a  $K_D$  of at least 20 nM, at least 40 nM, at least 60 nM, at least 80 nM, at least 100 nM, at least 120 nM, at least 140 nM, at least 160 nM, or at least 180 nM.

“EGFR,” “HER-1” or “erbB-1” refer to the art-recognized human epidermal growth factor receptor, erbB-1 (cDNA: NM\_005228, SEQ ID NO:5; protein: NP\_005219, SEQ ID 30 NO:6), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

“ΔEGFR” refers to the art-recognized receptor, ΔEGFR (cDNA: SEQ ID NO:7; protein: SEQ ID NO:8) (*see* Ekstrand et al., *PNAS* 89:4309-4313, 1992; and Nishikawa et al., *PNAS*



91:7727-7731, 1994) (comprising a deletion in the ECD; cDNA positions 275 through 1075, corresponding to exons 2-7 of the EGFR gene), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

5 “HER-2” or “erbB-2” refers to the art-recognized human receptor, erbB-2 (cDNA: NM\_004448, SEQ ID NO:9; protein: NP\_004439, SEQ ID NO:10), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

“HER-3” or “erbB-3” refers to the art-recognized human receptor, erbB-3 (cDNA: NM\_001982, SEQ ID NO:11; protein: NP\_001973, SEQ ID NO:12), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

10 The phrase “mutant form of HER-3” refers to a HER-3 protein having a substitution of Glu for Gly in the ectodomain of HER-3 corresponding to a single point mutation at nucleotide position 1877 (“a” instead of “g” at this position), resulting in substitution of Glu instead of Gly at residue position 560) (cDNA: SEQ ID NO:13; protein: SEQ ID NO:14).

15 “HER-4” or “erbB-4” refers to the art-recognized human receptor, erbB-4 (cDNA: NM\_005235, SEQ ID NO:15; protein: NP\_005226, SEQ ID NO:16), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

“IGF-1R” refers to the art recognized insulin-like growth factor 1 receptor (cDNA: NM\_000875, SEQ ID NO:17; protein: NP\_000866, SEQ ID NO:18), and including herstatin -, and/or Int8 RBD polypeptide-binding variants thereof.

20 As used herein, a pharmaceutical effect refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

25 As used herein therapeutic effect means an effect resulting from treatment of a subject that alters, typically improves or ameliorates the symptoms of a disease or condition or that cures a disease or condition. A therapeutically effective amount refers to the amount of a composition, molecule or compound which results in a therapeutic effect following administration to a subject.

As used herein, the term "subject" refers to animals, including mammals, such as human beings. As used herein, a patient refers to a human subject.

As used herein, the phrase "associated with" refers to certain biological aspects such as expression of a receptor or signaling by a receptor that occurs in the context of a disease or condition. Such biological aspect may or may not be causative or integral to the disease or condition but merely an aspect of the disease or condition.

As used herein, a biological activity refers to a function of a polypeptide including but not limited to complexation, dimerization, multimerization, receptor-associated kinase activity, receptor-associated protease activity, phosphorylation, dephosphorylation, autophosphorylation, ability to form complexes with other molecules, ligand binding, catalytic or enzymatic activity, activation including auto-activation and activation of other polypeptides, inhibition or modulation of another molecule's function, stimulation or inhibition of signal transduction and/or cellular responses such as cell proliferation, migration, differentiation, and growth, degradation, membrane localization, membrane binding, and oncogenesis. A biological activity can be assessed by assays described herein and by any suitable assays known to those of skill in the art, including, but not limited to *in vitro* assays, including cell-based assays, *in vivo* assays, including assays in animal models for particular diseases.

**TABLE 1.** Summary of SEQ ID NOS and accession numbers:

<b>MOLECULE</b>	<b>cDNA</b>	<b>PROTEIN</b>
RBD Int8 polypeptide(s))		SEQ ID NO:1
Herstatin (s)		SEQ ID NO:2
Mutant Int8 RBD polypeptide(s)		SEQ ID NO:3
Mutant Herstatin (s)		SEQ ID NO:4
EGFR (HER-1 or erbB-1)	SEQ ID NO:5 (NM_005228)	SEQ ID NO:6 (NP_005219)
$\Delta$ EGFR	SEQ ID NO:7	SEQ ID NO:8
HER-2 (erbB-2)	SEQ ID NO:9 (NM_004448)	SEQ ID NO:10 (NP_004439)
HER-3 (erbB-3)	SEQ ID NO:11 (NM_001982)	SEQ ID NO:12 (NP_001973)
Mutant form of HER-3	SEQ ID NO:13	SEQ ID NO:14

MOLECULE	cDNA	PROTEIN
HER-4 (erbB-4)	SEQ ID NO:15 (NM_005235)	SEQ ID NO:16 (NP_005226)
IGF-1R	SEQ ID NO:17 (NM_000875)	SEQ ID NO:18 (NP_000866)

#### Herstatin and/or RBD Int8 polypeptides and therapeutic agents

In preferred aspects, the present invention provides for the use of herstatin (SEQ ID NO:2), and variants and polypeptides thereof that bind to a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR). Also provided are uses of RBD Int8 polypeptides (SEQ ID NO:2), and receptor-binding variants and polypeptides thereof that bind to a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR).

Preferably, the herstatin, or variant thereof comprises an amino acid sequence of SEQ ID NO:2 (or of SEQ ID NO:2 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions), or a fragment of a sequence of SEQ ID NO:2 (or of SEQ ID NO:2 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions) of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present, and wherein the polypeptide binds to the extracellular domain (ECD) of a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR) with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}$ , or at least  $10^8 \text{ M}^{-1}$ . Preferably, the herstatin, or variant thereof, is from about 350 to 419 contiguous residues in length. Preferably, the herstatin, or variant thereof, binds to the extracellular domain (ECD) of a target receptor (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR) with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}$ , or at least  $10^8 \text{ M}^{-1}$ . Preferably, herstatin, or variant thereof, comprises a sequence of SEQ ID NO:2, or a conservative amino acid substitution variant thereof.

Preferably, the RBD Int8 polypeptides, and variants thereof, comprise an amino acid sequence of SEQ ID NO:1 (or of SEQ ID NO:1 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions), or a fragment of a sequence of SEQ ID NO:1 (or of SEQ ID NO:1 having from 1, to about 3, to about 5, to about 10, or to about 20

conservative amino acid substitutions) of about 50 to 79 contiguous residues in length, wherein the polypeptide binds to the extracellular domain (ECD) of a target receptor (e.g., EGFR, HER-2, HER-3, DEGRF, HER-4 and IGF-IR) with an affinity binding constant of about  $10^7 \text{ M}^{-1}$ , about  $5 \times 10^7 \text{ M}^{-1}$ , about  $10^8 \text{ M}^{-1}$ , or greater (or at least  $10^7 \text{ M}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}$ , or at least  $10^8 \text{ M}^{-1}$ ). Preferably, the RBD Int8 polypeptide, or variant thereof is from about 69 to 79 contiguous residues in length with a target receptor (e.g., EGFR, HER-2, HER-3, DEGRF, HER-4 and IGF-IR) affinity binding constant of about  $10^7 \text{ M}^{-1}$ , about  $5 \times 10^7 \text{ M}^{-1}$ , about  $10^8 \text{ M}^{-1}$ , or greater (or at least  $10^7 \text{ M}^{-1}$ , at least  $5 \times 10^7 \text{ M}^{-1}$ , or at least  $10^8 \text{ M}^{-1}$ ). Preferably, the RBD Int8 polypeptide, or variant thereof comprises a sequence of SEQ ID NO:1, or a conservative amino acid substitution variant thereof.

#### Specific Exemplary Embodiments:

##### *Methods of treatment using a herstatin, or a variant thereof*

A preferred embodiment of the present invention provides a method for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising administering to a subject in need thereof, a therapeutically effective amount of a herstatin, or of a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell of the subject, wherein the at least one target receptor is selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

In particular embodiments, the condition is a cellular proliferative condition or disorder, and preferably, the cellular proliferative condition or disorder is cancer.

In other embodiments, the target cell further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length. Preferably, the herstatin, or variant thereof comprises the C-terminal 79 contiguous amino acids of SEQ ID NO:2, and binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ .

Further embodiment provide for application of the methods in instances where the cancer

is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different than herstatin, herstatin variants, int8 RDB polypeptides, and  
5 int8 RDB polypeptide variants.

Additional embodiments further comprise administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular domain of a cellular receptor of the target cell. Preferably, the receptor-specific antibody binds to a cellular receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-  
10 3 (erbB-3); HER-4 (erbB-4) and IGF-1. In particular embodiments, the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5 (HERCEPTIN<sup>TM</sup>). In alternate embodiments, the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the herstatin, or the variant thereof. Preferably, the at least one other agent comprises a receptor-specific antibody, or a small-  
15 molecule receptor tyrosine kinase inhibitor.

Yet further embodiments comprise administration of a therapeutically effective amount of a chemotherapeutic agent. In particular embodiments, the chemotherapeutic agent is an anti-neoplastic agent selected from the group consisting of: cyclophosphamide, triethylenephosphoramide, triethylenethiophosphoramide, flutamide, altretamine,  
20 triethylenemelamine, trimethylolmelamine, meturedopa, uredopa, aminogluthetamide, L-asparaginase, BCNU, benzodopa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone,  
25 novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

In preferred embodiments, the herstatin, or variant thereof, comprises SEQ ID NO:23, which corresponds to the most common herstatin sequence (wild-type).

*Methods of treatment using an Int8 RBD polypeptide, or a variant thereof*

Alternate preferred embodiments provide a method for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising administering  
5 to a subject in need thereof, a therapeutically effective amount of an Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell of the subject, wherein the at least one target receptor is selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

In particular embodiments, the condition is a cellular proliferative condition or disorder,  
10 and preferably the cellular proliferative condition or disorder is cancer.

In additional embodiments, the target cell further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1  
15 of about 50 to 79 contiguous residues in length. Preferably, the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ .

Further embodiments provide for application of the methods where the cancer is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is  
20 specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different than herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants. Preferably, the at least one other agent comprises a receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

25 Additional embodiments further comprise administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular domain of a cellular receptor of the target cell. In particular embodiments, the receptor-specific antibody binds to a cellular receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1. In a particular embodiment, the

receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5 (HERCEPTIN<sup>TM</sup>). In alternate embodiments, the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the Int8 RBD polypeptide, or the variant thereof.

5 Yet additional embodiments further comprise administration of a therapeutically effective amount of a chemotherapeutic agent, and in particular embodiments, the chemotherapeutic agent is an anti-neoplastic agent selected from the group consisting of: cyclophosphamide, triethylenephosphoramidate, triethylenethiophosphoramidate, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedapa, uredepa,  
10 aminogluthethimide, L-asparaginase, BCNU, benzodepa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine,  
15 procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

In preferred embodiments, the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24, which corresponds to the most common Int8 RBD polypeptide sequence (wild-type).

## 20 *Methods of cellular targeting*

Yet further embodiments provide a method for targeting a therapeutic agent to target cells, comprising attaching the therapeutic agent to herstatin, or to a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell, wherein the at least one target receptor is selected from the group consisting of: ΔEGFR; HER-3 (erbB-3); HER-4 (erbB-  
25 4) and IGF-1.

In particular embodiments, the target cell is a cancer cell.

In other embodiments the target cell optionally further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, the herstatin, or variant thereof, comprises a polypeptide

selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length. Preferably, the herstatin, or variant thereof comprises the C-terminal 79 contiguous amino acids of SEQ ID NO:2, and binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ .

5 Alternate embodiments provide a method for targeting a therapeutic agent to target cells, comprising attaching the therapeutic agent to an Int8 RBD polypeptide, or to a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell, wherein the at least one target receptor is selected from the group consisting of:  $\Delta\text{EGFR}$ ; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

10 In particular embodiments, the target cell is a cancer cell.

In other embodiments, the target cell further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1  
15 of about 50 to 79 contiguous residues in length. Preferably, the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ .

#### *Pharmaceutical compositions*

20 Yet additional embodiments provide pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, an agent selected from the group consisting of: (a) herstatin, or a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell, wherein the at least one target receptor is selected from the  
25 group consisting of:  $\Delta\text{EGFR}$ ; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1; (b) a Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell, wherein the at least one target receptor is selected from the group consisting of:  $\Delta\text{EGFR}$ ; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1; (c) a receptor-specific antibody that binds to the extracellular domain (ECD) of a cellular receptor of the target cell;



and (d) combinations thereof, with the proviso that where the composition comprises the target cell receptor-specific antibody it also comprises at least one of the agents of (a) or (b).

Additional embodiments provide for a pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, a first agent selected from the group consisting of: herstatin, or a variant thereof; a Int8 RBD polypeptide, or a variant thereof; and combinations thereof, the composition further comprising a second agent selected from the group consisting of: a receptor-specific antibody that binds to the extracellular domain (ECD) of a cellular receptor of the target cell; a small molecule receptor tyrosine kinase inhibitor; and combinations thereof, with the proviso that the receptor-specific antibody is not a HER-1 or HER-2-specific antibody.

Preferably, the herstatin, or variant thereof, comprises SEQ ID NO:23. Preferably, the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

In particular embodiments, the condition treated with the composition is a cellular proliferative condition or disorder, and preferably the cellular proliferative condition or disorder is cancer.

In additional embodiments, the target cell further expresses EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

In particular embodiments, when agent (c) is present, the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the other agents (a) or (b).

In preferred embodiments agent (a) the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, and agent (b) the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

Further embodiments provide for a pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, a polynucleotide that encodes a

herstatin, or a herstatin variant.

Yet further embodiments provide for a pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, a polynucleotide that  
5 encodes an int8 RBD polypeptide, or an int8 RBD polypeptide variant.

#### *Mutant/variant HER-3 screening assays*

Particular embodiments provide for a method for identification of cells having HER-3 receptors that do not bind herstatin, int 8 RDB polypeptides, or variants thereof, comprising:  
10 obtaining a cellular sample; and determining, using one or more suitable assays, whether the cells express SEQ ID NO:14.

Additional embodiments provide for screening for cells that are, at least to some extent, non-responsive to herstatin, int 8 RDB polypeptides, or variants thereof, comprising obtaining a cellular sample; and determining, using one or more suitable assays, wherein the cells are  
15 determined to be at least to some extent, non-responsive to herstatin, int 8 RDB polypeptides, or variants thereof, express SEQ ID NO:14, wherein if the cells express SEQ ID NO:14.

#### Biologically Active Variants

Functional herstatin, functional herstatin variants, functional Int8 RBD polypeptides, and  
20 functional Int8 RBD polypeptide variants are those proteins that display one or more of the biological activities of herstatin, including but not limited to target receptor binding, inhibition of receptor dimerization, modulation of receptor-mediated signal transduction, modulation of receptor activation, receptor down-regulation, etc.

Variants of herstatin and/or RBD Int8 polypeptide have utility for aspects of the present  
25 invention. Variants can be naturally or non-naturally occurring. Naturally occurring variants (e.g., polymorphisms) are found in humans or other species and comprise amino acid sequences which are substantially identical to the amino acid sequence shown in SEQ ID NO:1 or 2. Species homologs of the protein can be obtained using subgenomic polynucleotides of the invention, as described below, to make suitable probes or primers for screening cDNA

expression libraries from other species, such as mice, monkeys, yeast, or bacteria, identifying cDNAs which encode homologs of the protein, and expressing the cDNAs as is known in the art.

Non-naturally occurring variants which retain substantially the same biological activities as naturally occurring protein variants, specifically the target RBD activity and the modulation of target receptor signaling activity, are also included here. Preferably, naturally or non-naturally occurring variants have amino acid sequences which are at least 85%, 90%, or 95% identical to the amino acid sequence shown in SEQ ID NOS:1 or 2. More preferably, the molecules are at least 98% or 99% identical. Percent identity is determined using any method known in the art. A non-limiting example is the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1. The Smith-Waterman homology search algorithm is taught in Smith and Waterman, *Adv. Appl. Math.* 2:482-489, 1981.

As used herein, "amino acid residue" refers to an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are generally in the "L" isomeric form. Residues in the "D" isomeric form can be substituted for any L-amino acid residue, as long as the desired functional property is retained by the polypeptide. NH<sub>2</sub> refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in J. Biol. Chem., 243:3552-59 (1969) and adopted at 37 C.F.R., §§. 1.821 - 1.822, abbreviations for amino acid residues are shown in Table 2:

**TABLE 2 – Table of Correspondence**

<b>SYMBOL</b>		
<b>1-Letter</b>	<b>3-Letter</b>	<b>AMINO ACID</b>
Y	Tyr	Tyrosine
G	Gly	Glycine
F	Phe	Phenylalanine
M	Met	Methionine

<b>SYMBOL</b>		
<b>1-Letter</b>	<b>3-Letter</b>	<b>AMINO ACID</b>
A	Ala	Alanine
S	Ser	Serine
I	Ile	Isoleucine
L	Leu	Leucine
T	Thr	Threonine
V	Val	Valine
P	Pro	Proline
K	Lys	Lysine
H	His	Histidine
Q	Gln	Glutamine
E	Glu	glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	Tryptophan
R	Arg	Arginine
D	Asp	aspartic acid
N	Asn	Asparagines
B	Asx	Asn and/or Asp
C	Cys	Cysteine
X	Xaa	Unknown or other

It should be noted that all amino acid residue sequences represented herein by a formula have a left to right orientation in the conventional direction of amino-terminus to carboxyl-terminus. In addition, the phrase "amino acid residue" is defined to include the amino acids listed in the Table of Correspondence and modified and unusual amino acids, such as those referred to in 37 C.F.R. §§ 1.821-1.822, and incorporated herein by reference. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues or to an amino-terminal group such as NH<sub>2</sub> or to a carboxyl-terminal group such as COOH.

Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological or immunological activity can be found using computer

programs well known in the art, such as DNASTAR software. Preferably, amino acid changes in the protein variants disclosed herein are conservative amino acid changes, *i.e.*, substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate),  
5 basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

10 It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting variant.

Variants of the herstatin and/or RBD Int8 polypeptide disclosed herein include  
15 glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties (*e.g.*, pegylated molecules). Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art. Variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions which do not affect functional activity of the  
20 proteins are also variants.

A subset of mutants, called muteins, is a group of polypeptides in which neutral amino acids, such as serines, are substituted for cysteine residues which do not participate in disulfide bonds. These mutants may be stable over a broader temperature range than native secreted proteins (see, *e.g.*, Mark *et al.*, United States Patent No. 4,959,314).

25 Preferably, amino acid changes in the herstatin and/or RBD Int8 polypeptide variants are conservative amino acid changes, *i.e.*, substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar

(alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

5 It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting secreted protein or polypeptide variant. Properties and functions of herstatin and/or RBD Int8 polypeptide protein or polypeptide variants are of the same type as a  
10 protein comprising the amino acid sequence encoded by the nucleotide sequence shown in SEQ ID NO:1 or 2, although the properties and functions of variants can differ in degree.

Herstatin and/or RBD Int8 polypeptide variants include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties (*e.g.*, pegylated molecules). Herstatin and/or RBD Int8 polypeptide variants also include allelic  
15 variants, species variants, and muteins. Truncations or deletions of regions which do not affect functional activity of the proteins are also variants. Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art.

It will be recognized in the art that some amino acid sequences of the herstatin and/or  
20 RBD Int8 polypeptides of the invention can be varied without significant effect on the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there are critical areas on the protein which determine activity. In general, it is possible to replace residues that form the tertiary structure, provided that residues performing a similar function are used. In other instances, the type of residue may be completely unimportant  
25 if the alteration occurs at a non-critical region of the protein. The replacement of amino acids can also change the selectivity of binding to cell surface receptors (Ostade et al., *Nature* 361:266-268, 1993). Thus, the herstatin and/or RBD Int8 polypeptides of the present invention may include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation.

Of particular interest are substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids. The latter results in proteins with reduced positive charge to improve the characteristics of the disclosed protein. The prevention of aggregation is highly desirable. Aggregation of proteins not only results in a loss of activity but can also be problematic when preparing pharmaceutical formulations, because they can be immunogenic (see, e.g., Pinckard et al., *Clin. Exp. Immunol.* 2:331-340 (1967); Robbins et al., *Diabetes* 36:838-845 (1987); and Cleland et al., *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993)).

Amino acids in the herstatin and/or RBD Int8 polypeptides of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as binding to a natural or synthetic binding partner. Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., *J. Mol. Biol.* 224:899-904 (1992) and de Vos et al. *Science* 255:306-312 (1992)).

As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein. Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of substitutions for any given herstatin and/or RBD Int8 polypeptide will not be more than 50, 40, 30, 25, 20, 15, 10, 5 or 3.

In addition, pegylation of herstatin and/or RBD Int8 polypeptides and/or muteins is expected to provide such improved properties as increased half-life, solubility, and protease resistance. Pegylation is well known in the art.

### Fusion Proteins

Fusion proteins comprising proteins or polypeptide fragments of herstatin and/or RBD Int8 polypeptide can also be constructed. Fusion proteins are useful for generating antibodies

against amino acid sequences and for use in various targeting and assay systems. For example, fusion proteins can be used to identify proteins which interact with a herstatin and/or RBD Int8 polypeptide of the invention or which interfere with its biological function. Physical methods, such as protein affinity chromatography, or library-based assays for protein-protein interactions, such as the yeast two-hybrid or phage display systems, can also be used for this purpose. Such methods are well known in the art and can also be used as drug screens. Fusion proteins comprising a signal sequence can be used.

A fusion protein comprises two protein segments fused together by means of a peptide bond. Amino acid sequences for use in fusion proteins of the invention can be utilize the amino acid sequence shown in SEQ ID NO:1 or 2 or can be prepared from biologically active variants of SEQ ID NO:1 or 2, such as those described above. The first protein segment can include of a full-length herstatin and/or RBD Int8 polypeptide.

Other first protein segments can consist of about 50 to about 79 contiguous amino acids from SEQ ID NO:1, or, with respect to SEQ ID NO:2, from about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids of SEQ ID NO:2 are present, or from about 350 to 419 contiguous residues in length wherein the C-terminal 79 contiguous amino acids of SEQ ID NO:2 are present.

The second protein segment can be a full-length protein or a polypeptide fragment. Proteins commonly used in fusion protein construction include  $\beta$ -galactosidase,  $\beta$ -glucuronidase, green fluorescent protein (GFP), autofluorescent proteins, including blue fluorescent protein (BFP), glutathione-S-transferase (GST), luciferase, horseradish peroxidase (HRP), and chloramphenicol acetyltransferase (CAT). Additionally, epitope tags can be used in fusion protein constructions, including histidine (His) tags, FLAG tags, influenza hemagglutinin (HA) tags, Myc tags, VSV-G tags, and thioredoxin (Trx) tags. Other fusion constructions can include maltose binding protein (MBP), S-tag, Lex a DNA binding domain (DBD) fusions, GAL4 DNA binding domain fusions, and herpes simplex virus (HSV) BP16 protein fusions.

These fusions can be made, for example, by covalently linking two protein segments or by standard procedures in the art of molecular biology. Recombinant DNA methods can be used to prepare fusion proteins, for example, by making a DNA construct which comprises a coding



region for the protein sequence of SEQ ID NO:1 or 2 in proper reading frame with a nucleotide encoding the second protein segment and expressing the DNA construct in a host cell, as is known in the art. Many kits for constructing fusion proteins are available from companies that supply research labs with tools for experiments, including, for example, Promega Corporation (Madison, WI), Stratagene (La Jolla, CA), Clontech (Mountain View, CA), Santa Cruz Biotechnology (Santa Cruz, CA), MBL International Corporation (MIC; Watertown, MA), and Quantum Biotechnologies (Montreal, Canada; 1-888-DNA-KITS).

### Cell Targeting

According to particular aspects of the present invention, herstatin- and/or RBD Int8 polypeptide-based agents can be used to target EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R on cells (*e.g.*, cancer cells). Herstatin- and/or RBD Int8 polypeptide-based agents can be used to deliver a locally acting biological agent that will affect the targeted cell.

Each of the target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R) is expressed on the surface of cells and are accessible to exogenous molecules. Where any of these target receptors are present at higher levels on cancer cells as compared to non-cancer cells, they can be utilized as preferential targets for systemic herstatin- and/or RBD Int8 polypeptide-based agents -based therapies. The differential expression of these target receptors enables the specificity of herstatin- and/or RBD Int8 polypeptide-based agents-based therapy. Herstatin- and/or RBD Int8 polypeptide-based cytotoxic agents directed against the target receptor preferentially affect cancer cells over normal tissue. For example, an herstatin- or RBD Int8 polypeptide-radioisotope conjugate that binds a target receptor (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-1R) present predominantly on cancer cells would be expected to selectively affect those cells within a treated individual. Preferably, the target is accessible to the herstatin- and/or RBD Int8 polypeptide-based agent, and is found in substantially greater concentrations on the targeted cancer cells than non-cancer cells.

Therefore, the present invention includes<sup>TM</sup>- and/or RBD Int8 polypeptide-based agents

specific to one or more of the target receptors that will enable or facilitate treatment of cancer.

In particular aspects, herstatin- and/or RBD Int8 polypeptides are conjugated or coupled to toxins.

In alternate embodiments, herstatin- and/or RBD Int8 polypeptides are conjugated or  
5 coupled to radionuclides.

Additional embodiments provide for herstatin- and/or RBD Int8 polypeptide-coated liposomes which contain one or more biologically active compounds.

In particular aspects, binding of an herstatin- and/or RBD Int8 polypeptide-agent to a cell is sufficient to inhibit growth (*e.g.*, cytostatic effects) or kill the target cell (cytotoxic effects).

10 The mechanism of these activities may vary, but may involve herstatin- and/or RBD Int8 polypeptide-dependent cell-mediated cytotoxicity, activation of apoptosis, inhibition of ligand-receptor function, or provide a signal for complement fixation. In fact, herstatin- and/or RBD Int8 polypeptide-agents may exhibit one or several of such activities. In particular aspects, herstatin- and/or RBD Int8 polypeptide-agents are cytostatic, but not cytotoxic. Preferably,  
15 herstatin and/or RBD Int8 polypeptide-agents bind to target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4),  $\Delta$ EGFR or IGF-1R), and are either cytotoxic or cytostatic.

In particular embodiments, herstatin- and/or RBD Int8 polypeptide-agents can be conjugated or coupled to a diverse array of compounds which include, but are not limited to  
20 proteins, toxins or cytotoxic agents, radionuclides, apoptotic factors), anti-angiogenic compounds or other biologically active compounds which will inhibit the growth of or kill the target cell or tissue. For example, cytotoxic or cytostatic agents include, but are not limited to, diphtheria toxin and Pseudomonas exotoxin, ricin, gelonin, doxorubicin and its derivatives, iodine-131, yttrium-90, indium-111, RNase, calicheamicin, apoptotic agents, and  
25 antiangiogenic agents. According to aspects of the present invention, herstatin- and/or RBD Int8 polypeptides coupled to these compounds are used to adversely affect cells displaying one or more target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4),  $\Delta$ EGFR or IGF-1R).

Toxins can also be targeted to specific cells by incorporation of the toxin into herstatin-

and/or RBD Int8 polypeptide-coated liposomes. The herstatin- and/or RBD Int8 polypeptide-based agent directs the liposome to the target cell where the bioactive compound is released. For example, cytotoxins in herstatin- and/or RBD Int8 polypeptide-coated liposomes are used to treat cancer. In alternate embodiments, these targeted liposomes are loaded with DNA encoding  
5 bioactive polypeptides (*e.g.*, inducible nitric oxide synthase).

Prodrugs or enzymes can also be delivered to targeted cells by specific herstatin- and/or RBD Int8 polypeptide-agents. In this case the herstatin conjugate consists of an herstatin- and/or RBD Int8 polypeptide-based agent coupled to a drug that can be activated once the antibody binds the target cell. Examples of this strategy using antibodies have been reviewed  
10 (*e.g.*, Denny 2001; and Xu and McLeod 2001).

Therefore, in particular embodiments, herstatin- and/or RBD Int8 polypeptide-prodrug/enzyme conjugates targeted to one or more target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4),  $\Delta$ EGFR or IGF-1R) have utility for the treatment of cancer.

15 The specificity and high affinity of the herstatin- and/or RBD Int8 polypeptide-based agents makes them ideal candidates for delivery of toxic agents to a specific subset of cellular targets. Preferably, one or more target receptors (*e.g.*, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4),  $\Delta$ EGFR or IGF-1R) are present at higher levels on the target cells (*e.g.*, cancer, tumor cells) than on non-cancer cells.

20

#### Pharmaceutical Compositions and Therapeutic Uses

Pharmaceutical compositions of the invention can comprise herstatin and/or RBD Int8 polypeptides, or herstatin- and/or RBD Int8 polypeptide-based agents of the claimed invention in a therapeutically effective amount. The term "therapeutically effective amount" as used  
25 herein refers to an amount of a therapeutic agent to treat, ameliorate, or prevent a desired disease or condition, or to exhibit a detectable therapeutic or preventative effect. The effect can be detected by, for example, chemical markers or antigen levels. Therapeutic effects also include reduction in physical symptoms. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition, and the therapeutics or

combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance. However, the effective amount for a given situation is determined by routine experimentation and is within the judgment of the clinician. For purposes of the present invention, an effective dose will generally be from about 0.01 mg/ kg to 50 mg/kg or  
5 0.05 mg/kg to about 10 mg/kg of the herstatin and/or RBD Int8 polypeptide constructs in the individual to which it is administered. A non-limiting example of a pharmaceutical composition is a composition that either enhances or diminishes signaling mediated by the inventive target receptors (*e.g.*, EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR). Where such signaling promotes a disease-related process, modulation of the signaling would be the goal of the  
10 therapy.

A pharmaceutical composition can also contain a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic agent, such as antibodies or a polypeptide, genes, and other therapeutic agents. The term refers to any pharmaceutical carrier that does not itself induce the production of antibodies  
15 harmful to the individual receiving the composition, and which can be administered without undue toxicity. Suitable carriers can be large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Such carriers are well known to those of ordinary skill in the art. Pharmaceutically acceptable carriers in therapeutic compositions can include  
20 liquids such as water, saline, glycerol and ethanol. Auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, can also be present in such vehicles. Typically, the therapeutic compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. Liposomes are included within the definition of a  
25 pharmaceutically acceptable carrier. Pharmaceutically acceptable salts can also be present in the pharmaceutical composition, *e.g.*, mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. A thorough discussion of pharmaceutically acceptable excipients is available in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., New Jersey,

1991).

Delivery Methods. Once formulated, the compositions of the invention can be administered directly to the subject or delivered *ex vivo*, to cells derived from the subject (*e.g.*, as in *ex vivo* gene therapy). Direct delivery of the compositions will generally be accomplished  
5 by parenteral injection, *e.g.*, subcutaneously, intraperitoneally, intravenously or intramuscularly, myocardial, intratumoral, peritumoral, or to the interstitial space of a tissue. Other modes of administration include oral and pulmonary administration, suppositories, and transdermal applications, needles, and gene guns or hypodermic sprays. Dosage treatment can be a single dose schedule or a multiple dose schedule.

10 Methods for the *ex vivo* delivery and reimplantation of transformed cells into a subject are known in the art and described in *e.g.*, International Publication No. WO 93/14778. Examples of cells useful in *ex vivo* applications include, for example, stem cells, particularly hematopoietic, lymph cells, macrophages, dendritic cells, or tumor cells. Generally, delivery of nucleic acids for both *ex vivo* and *in vitro* applications can be accomplished by, for example,  
15 dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, direct microinjection of the DNA into nuclei, and viral-mediated, such as adenovirus or alphavirus, all well known in the art.

In a preferred embodiment, disorders of proliferation, such as cancer, can be amenable to  
20 treatment by administration of a therapeutic agent based on the provided polynucleotide or corresponding polypeptide. The therapeutic agent can be administered in conjunction with one or more other agents including, but not limited to, receptor-specific antibodies and/or chemotherapeutic (*e.g.*, anti-neoplastic agents). Administered "in conjunction" includes administration at the same time, or within 1 day, 12 hours, 6 hours, one hour, or less than one  
25 hour, as the other therapeutic agent(s). The compositions may be mixed for co-administration, or may be administered separately by the same or different routes.

The dose and the means of administration of the inventive pharmaceutical compositions are determined based on the specific qualities of the therapeutic composition, the condition, age, and weight of the patient, the progression of the disease, and other relevant factors. For

example, administration of polynucleotide therapeutic compositions agents of the invention includes local or systemic administration, including injection, oral administration, particle gun or catheterized administration, and topical administration. The therapeutic polynucleotide composition can contain an expression construct comprising a promoter operably linked to a polynucleotide encoding, for example, SEQ ID NO:2, or encoding about 80 to 419 (or about 350 to 419) contiguous amino acids of SEQ ID NO:2. Various methods can be used to administer the therapeutic composition directly to a specific site in the body. For example, a small metastatic lesion is located and the therapeutic composition injected several times in several different locations within the body of tumor. Alternatively, arteries which serve a tumor are identified, and the therapeutic composition injected into such an artery, in order to deliver the composition directly into the tumor. A tumor that has a necrotic center is aspirated and the composition injected directly into the now empty center of the tumor. X-ray imaging is used to assist in certain of the above delivery methods.

Herstatin and/or RBD Int8 polypeptide-mediated targeted delivery of therapeutic agents to specific tissues can also be used. Receptor-mediated DNA delivery techniques are described in, for example, Findeis et al., *Trends Biotechnol.* (1993) 11:202; Chiou et al., *Gene Therapeutics: Methods And Applications Of Direct Gene Transfer* (J.A. Wolff, ed.) (1994); Wu et al., *J. Biol. Chem.* (1988) 263:621; Wu et al., *J. Biol. Chem.* (1994) 269:542; Zenke et al., *Proc. Natl. Acad. Sci. (USA)* (1990) 87:3655; Wu et al., *J. Biol. Chem.* (1991) 266:338. Therapeutic compositions containing a polynucleotide are administered in a range of about 100 ng to about 200 mg of DNA for local administration in a gene therapy protocol. Concentration ranges of about 500 ng to about 50 mg, about 1 mg to about 2 mg, about 5 mg to about 500 mg, and about 20 mg to about 100 mg of DNA can also be used during a gene therapy protocol. Factors such as method of action (e.g., for enhancing or inhibiting levels of the encoded gene product) and efficacy of transformation and expression are considerations which will affect the dosage required for ultimate efficacy of the subgenomic polynucleotides. Where greater expression is desired over a larger area of tissue, larger amounts of subgenomic polynucleotides or the same amounts readministered in a successive protocol of administrations, or several administrations to different adjacent or close tissue portions of, for example, a tumor site, may

be required to effect a positive therapeutic outcome. In all cases, routine experimentation in clinical trials will determine specific ranges for optimal therapeutic effect.

The therapeutic polynucleotides and polypeptides of the present invention can be delivered using gene delivery vehicles. The gene delivery vehicle can be of viral or non-viral origin (see generally, Jolly, *Cancer Gene Therapy* (1994) 1:51; Kimura, *Human Gene Therapy* (1994) 5:845; Connelly, *Human Gene Therapy* (1995) 1:185; and Kaplitt, *Nature Genetics* (1994) 6:148). Expression of such coding sequences can be induced using endogenous mammalian or heterologous promoters. Expression of the coding sequence can be either constitutive or regulated.

Viral-based vectors for delivery of a desired polynucleotide and expression in a desired cell are well known in the art. Exemplary viral-based vehicles include, but are not limited to, recombinant retroviruses (see, e.g., WO 90/07936; WO 94/03622; WO 93/25698; WO 93/25234; U.S. Patent No. 5,219,740; WO 93/11230; WO 93/10218; U.S. Patent No. 4,777,127; GB Patent No. 2,200,651; EP 0 345 242; and WO 91/02805), alphavirus-based vectors (e.g., Sindbis virus vectors, Semliki forest virus (ATCC VR-67; ATCC VR-1247), Ross River virus (ATCC VR-373; ATCC VR-1246) and Venezuelan equine encephalitis virus (ATCC VR-923; ATCC VR-1250; ATCC VR 1249; ATCC VR-532), and adeno-associated virus (AAV) vectors (see, e.g., WO 94/12649, WO 93/03769; WO 93/19191; WO 94/28938; WO 95/11984 and WO 95/00655). Administration of DNA linked to killed adenovirus as described in Curiel, *Hum. Gene Ther.* (1992) 3:147 can also be employed.

Non-viral delivery vehicles and methods can also be employed, including, but not limited to, polycationic condensed DNA linked or unlinked to killed adenovirus alone (see, e.g., Curiel, *Hum. Gene Ther.* (1992) 3:147); ligand-linked DNA (see, e.g., Wu, *J. Biol. Chem.* 264:16985 (1989)); eukaryotic cell delivery vehicles cells (see, e.g., U.S. Patent No. 5,814,482; WO 95/07994; WO 96/17072; WO 95/30763; and WO 97/42338) and nucleic charge neutralization or fusion with cell membranes. Naked DNA can also be employed. Exemplary naked DNA introduction methods are described in WO 90/11092 and U.S. Patent No. 5,580,859. Liposomes that can act as gene delivery vehicles are described in U.S. Patent No. 5,422,120; WO 95/13796; WO 94/23697; WO 91/14445; and EP 0524968. Additional approaches are

described in Philip, *Mol. Cell Biol.* 14:2411 (1994), and in Woffendin, *Proc. Natl. Acad. Sci.* (1994) 91:11581-11585.

Further non-viral delivery suitable for use includes mechanical delivery systems such as the approach described in Woffendin et al., *Proc. Natl. Acad. Sci. USA* 91(24):11581 (1994).

5 Moreover, the coding sequence and the product of expression of such can be delivered through deposition of photopolymerized hydrogel materials or use of ionizing radiation (see, e.g., U.S. Patent No. 5,206,152 and WO 92/11033). Other conventional methods for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene transfer particle gun (see, e.g., U.S. Patent No. 5,149,655); use of ionizing radiation for  
10 activating transferred gene (see, e.g., U.S. Patent No. 5,206,152 and WO 92/11033).

#### Exemplary Conditions Treatable and Combination Therapies

The present invention, for the first time, not only discloses that herstatin and/or the intron 8-encoded domain thereof (referred to herein as "int8 RBD" polypeptides), and variants thereof,  
15 not only bind with high affinity (e.g., at nM concentrations) to: all four of the ErbB receptors EGFR (HER-1, erbB-1), HER-2 (erbB-2), HER-3 (erbB-3), and HER-4 (erbB-4), and to  $\Delta$ EGFR and the IGF-1 receptor, but also discloses that such target receptor binding has novel and substantial utility to modulate intracellular signaling mediated by these receptors.

Therefore, the present invention encompasses a broad range of utilities, including  
20 therapeutic utilities. For example, particular embodiments provide novel methods and compositions for the treatment of cancer and other conditions and disorders characterized by target receptor expression or over-expression, and/or target receptor-mediated signaling or aberrant signaling.

Specific embodiments provide a method for treating cancer, comprising administering a  
25 therapeutically effective amount of herstatin, or of a variant thereof, that binds to the extracellular domain of a target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, wherein the cancer cells express at least one of the target receptors. Alternatively, a therapeutically effective amount of a Int8 RBD polypeptide, or of a variant thereof, that binds to the extracellular domain of a target



receptor selected from the group consisting of:  $\Delta$  EGFR; HER-3 (erbB-3); HER-4 (erbB-4), IGF-1R and combinations thereof, is administered. The methods also encompass treatments where the cancer cells further express EGFR (HER-1, erbB-1), HER-2 (erbB-2) or both.

Combination therapies are also encompassed by aspects of the present invention. For example, the inventive methods may further comprise administration of a therapeutically effective amount of: a receptor-specific antibody that binds to the extracellular domain of a target receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$  EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), and IGF-1R. Alternatively, the inventive methods may further comprise administration of chemotherapeutic agents, such as antineoplastic agents.

Examples of anti-neoplastic agents are cyclophosphamide, triethylenephosphoramidate, triethylenethiophosphoramidate, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedapa, uredapa, aminoglutethimide, L-asparaginase, BCNU, benzodepa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

*Treatment of refractory cancer.* By virtue of their activation of the PI3K and MAPK cascades and potentially other signal transduction pathways, both the EGF and IGF receptor families are major regulators of cell growth and survival, and dysregulation of either receptor family can lead to uncontrolled growth and tumorigenesis. Moreover, 'cross-talk' is believed to occur between these receptor families, and various studies support the concept that redundant signaling through IGF-1R maintains activation of critical pathways for survival in the presence of EGFR family inhibitors. Such cross-talk and redundant signaling has been shown to be involved in cancers that are, or that become refractory to treatment by, for example, a particular receptor-specific agent (e.g., antibody reagent, or small molecule receptor tyrosine kinase inhibitor) or class of agents; that is, such cancers do not respond, respond only weakly, or

progressively become less responsive to particular agents, by virtue of intracellular signaling mediated by a receptor other than the one being targeted by the particular agent. These findings all point to the need to for a multi-functional inhibitor that simultaneously targets both the EGF and IGF-IR families. Aspects of the present invention have met this need.

5       Accordingly, further embodiments provide for application of the methods where the cancer is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different than herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants. Preferably, the at least one other agent comprises a  
10       receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

      According to the present invention therefore, herstatin or Int8 RBD polypeptides, and variants thereof can be used in therapeutic methods and pharmaceutical compositions to treat a variety of conditions having an aspect related to, or associated with altered target receptor  
15       expression, altered target receptor expression, target receptor-mediated signaling, or altered target receptor-mediated signaling at a cellular level. Such methods comprising administering to a subject having such a condition, a therapeutically effective amount of a herstatin or Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one cellular target receptor.

20

      The present invention will now be illustrated by reference to the following examples which set forth particularly advantageous embodiments. However, it should be noted that these embodiments are illustrative and are not to be construed as restricting the invention in any way.

25

### **EXAMPLE 1** (Materials and Methods)

*Cell lines, transfections, expression vectors, western blots and antibodies*

*Cell lines.* The 3T3/HER-2 cells were previously described (Lin et al., *Mol. Cell. Endocrinol.*, 69:111-9, 1990). The 3T3/IGF-IR cells were from Dr. Charles Roberts, OHSU,  
30       Portland, OR. MCF7 breast carcinoma cells were obtained from the American Type Culture

Collection and maintained at 37°C/5% CO<sub>2</sub> in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) and gentamicin (0.25 µg/ml). Media and supplements were purchased from Gibco BRL-Life Technologies (Grand Island, NY). Hst-expressing MCF7 clones (previously characterized in Jhabvala-Romero et al., *Oncogene* 22:8178-86, 2003), were maintained under the same conditions as parental MCF7 cells in media supplemented with 0.5 mg/ml G418 sulfate.

*Transfections.* For transient transfections, 2 µg of empty vector or 2 µg EGFR, HER-2, HER-3, HER-4, ΔEGFR, or FGFR-3-myc expression vectors were added with Lipofectamine™ (GIBCO-BRL) to Cos-7 cells in 6 cm plates.

*Expression vectors.* The HER-2 and EGFR expression plasmids were previously described (Azios et al., *Oncogene* 20:5199-209, 2001), ΔEGFR was a gift from Dr. Webster Cavenne (Ludwig Institute for Cancer Research, UCSD, La Jolla, California), the FGFR-3-myc construct was from Dr. William Horton (Shriners Research Hospital, Portland, OR), and the HER-4 expression plasmid was a gift of Dr. Nancy Hynes (Friedrich Miescher-Institute for Biomedial Research, Basel, Switzerland).

*Antibodies.* Antibodies against the β-subunit of IGF-IR were from Dr. Charles Roberts (Oregon Health & Science University). All primary antibodies were used at a 1:1000 dilution and incubated with Western blots overnight at 4°C, unless otherwise indicated. Polyclonal antibodies (IGF-IR and IRS-1) and monoclonal antibody PY20 were obtained from Santa Cruz Biotechnology (Santa Cruz, CA). Monoclonal ERK 1/2 and polyclonal pERK 1/2 and Akt/PKB antibodies were purchased from Cell Signaling Technologies (Boston, MA). Monoclonal herstatin and polyclonal IRS-2 antibodies were obtained from Upstate Biotechnology (Lake Placid, NY). Polyclonal pAkt/PKB and pIGF-IR antibodies were purchased from Biosource International (Hopkinton, MA) and polyclonal anti-Shc antibody was obtained from Transduction Labs (Lexington, KY).

*Western blot analysis.* To analyze receptors by Western blot analysis, proteins were resolved by SDS-PAGE and electro-transferred onto nitrocellulose membranes (BioRad, Hercules, CA). Blots were blocked in 5% milk and incubated with primary antibody overnight at 4°C. The antibodies included anti-HER-2 (Christianson et al., *Cancer Res.* 58:5123-9, 1998)

and anti-EGFR, anti-HER-3, anti-HER-4, which were all rabbit polyclonal antibodies against the receptor C-terminal domains (Santa Cruz Biotechnology). After washing, the blots were incubated with secondary antibody conjugated to HRP for 30 min (BioRad, Hercules, CA). The membranes were developed with SuperSignal™ West Dura (Pierce, Rockford, IL) and exposed to x-ray film. In particular studies, cells were grown to ~80% confluency, serum-starved overnight in DMEM, and treated with 14 nM EGF, 5 nM IGF-I, or 20 nM IGF-II (in some experiments) for the times indicated. For Western immunoblots, cells were washed twice with ice-cold 1x PBS and lysed in 1x SDS sample buffer (Maniatis) without DTT or dye and boiled for 5 min. After clarification by centrifugation at 13,000 rpm for 5 min., protein concentration was determined using a detergent-compatible protein assay kit (Bio-Rad; Hercules, CA). DTT was then added to 100 mM and bromophenol blue to 0.1% (w/v) and samples were boiled again for 5 min. 20 mg protein was run on a 10% SDS-PAGE and blotted onto nitrocellulose (Amersham Pharmacia Biotech; Piscataway, NJ). Blots were probed with a phospho-specific antibody, stripped in 5x stripping buffer (Maniatis) and reprobed with the respective pan antibody. For immunoprecipitation, cells were washed twice with ice-cold 1x PBS, lysed in NP-40 lysis buffer [1% NP-40, 150 mM NaCl, 10% glycerol, 20 mM Tris-HCl (pH 8.0), 1 mM EDTA (pH 8.0), 0.2% SDS, complete protease inhibitors (Roche Diagnostics; Indianapolis, IN), 1 mM NaVO<sub>4</sub>, and 1 mg/ml pepstatin] and kept on ice for 30 min, inverting the tubes every 2 minutes. Lysates were then centrifuged at 13,000 rpm for 15 minutes and the supernatant transferred to a new tube. Protein concentration was determined as above. For IGF-IR, 1 mg of whole-cell lysate protein was immunoprecipitated with 16 mg of anti-IGF-IR antibody and incubated overnight at 4°C while rocking. For IRS-1 and IRS-2, 500 mg of whole-cell lysate protein was incubated overnight with 10 mg antibody. 100 ml of protein A-agarose bead slurry (Amersham Pharmacia Biotech) was added for 2 hours rocking at 4°C. Three washes were performed and the pellet was boiled in 2x SDS sample buffer (Maniatis). The beads were spun down and the supernatant loaded onto a 10% (IGF-IR) or 7% (IRS-1/2) SDS-PAGE and blotted as above. Blots were probed with PY20, stripped as above, and reprobed with their respective antibodies. Binding of primary antibodies was detected by enhanced chemiluminescence (Amersham), and film exposures were quantified using a scanning densitometer (Bio-Rad).

*Sequencing of human, monkey and rat Intron 8 regions:*

*Human.* Human genomic DNA was obtained from blood samples (supplied by Dr. David Henner, OHSU) from individuals 18 years or more, after giving informed consent, with approval by the Institutional Review Board of OHSU. The samples, assigned random four-digit numbers, could not be traced to patient identity. The polymerase chain reaction (PCR) was employed to amplify intron 8 using primers: 3' AACACAGCGGTGTGAGAAGTGC (exon 8) (SEQ ID NO:19) and 5' GTATCGGTAGTTCATTTCTTTGGTTGC (intron 9) (SEQ ID NO:20). The reactions were cycled (95°C for 2 minutes, 95°C for 30 seconds, 69°C for 30 seconds, 72°C for 30 seconds) for 30 cycles. PCR products were purified and subjected to cycle-sequencing. Electropherograms were individually reviewed to detect polymorphic alleles. Samples found to contain a polymorphism were sequenced at least once more to confirm the mutation.

*Monkey.* Rhesus monkey DNA, provided by Dr. Scott Wong (ORPC, Portland, OR) was amplified and sequenced using the above primers.

*Rat.* Intron 8 in rat genomic DNA (provided by Dr. John Adelman, Vollum Institute, Portland, OR) was amplified by PCR using rat specific primers: 5'-CTA CCT GTC TAC GGA AGT GG-3' (SEQ ID NO:21) and 5'-TTC CGG GCA GAA ATG CCA GG-3' (SEQ ID NO:22). The cycling parameters were: 94°C, 30"; 62° C, 30"; 72°C, 60", for 25 cycles.

*Expression and purification of intron 8-encoded peptide (Int8) and herstatin:*

*Receptor binding domain (RBD).* Intron 8 cDNA was cloned into the pET 30 bacterial expression vector (Novagen, Madison, WI), expressed in bacteria (BL-21), and purified by nickel affinity chromatography as described (Doherty et al., *Supra*).

*Herstatin.* For purification of insect herstatin, S2 insect cells, stably transfected with 6xHis tagged-herstatin in the pMT/BiP expression plasmid (Invitrogen, Carlsbad, CA), were induced with 100 µM cupric sulfate for about 16hrs. Herstatin was purified to about 90% purity

by Ni-NTA (Qiagen, Valencia, CA) affinity chromatography as previously described (Jhabvala-Romero et al. *Supra.*).

*Cell binding studies:*

5            *ELISA.* Monolayer cultures of  $\sim 2 \times 10^6$  cells were plated in 6-well tissue culture plates, and were incubated with purified herstatin or int8 peptide for 2 hours at 4°C in serum-free DMEM. Cells were washed with Phosphate Buffered Saline (PBS) and extracted in 50mM Tris-HCl, pH 7.0, 1.0% NP-40. Int8 peptide or herstatin bound to cells were quantified using a sandwich herstatin ELISA per manufacturer's instructions (Upstate Biotechnology, Lake Placid,  
10 NY).

The dissociation constant ( $K_D$ ) and maximal binding ( $B_{max}$ ) of herstatin or the int8 peptide were determined by nonlinear regression analysis of the plot of pmol of bound *versus* nM of herstatin or int8 peptide added. Statistical comparisons between different binding curves were performed by extra sums-of-squares F-test nonlinear regression coefficients. All tests were  
15 performed ( $\alpha = 0.05$ ) using GraphPad Prism 4™ software (GraphPad™ Software, 1994-2003).

*Pull-down assays with int8 peptide immobilized on protein S agarose:*

About 100  $\mu$ l of a 50% suspension of S-protein agarose (Novagen) was incubated with or without 100  $\mu$ g of int8 peptide with an S-protein tag, at room temperature for 1 hr, and then  
20 washed twice with 500  $\mu$ l PBS. The agarose samples were then incubated at room temperature for 1 hr with 200  $\mu$ g of transfected Cos-7 cell extract, then was washed twice with 500  $\mu$ l of PBS with 1% NP40. The proteins associated with the resin were eluted at 92°C for 2 min in 40 $\mu$ l of SDS-sample buffer, and analyzed as a Western blot.

*Growth assays.* Cells ( $4 \cdot 10^4$ ) were plated in quadruplicate in 24-well plates, incubated in  
25 serum-free DMEM for 24 hours, and treated with either 5 nM IGF-I (GroPep; Adelaide,

Australia) or 10 mM HCl as vehicle. Following serum starvation, and for four subsequent days at 24-hour intervals, cell monolayers were washed with PBS and incubated for 30 minutes at 37°C with 30 µl of MTS reagent [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl-2H-tetrazolium) inner salt Aqueous One Solution (Promega; Madison, WI) dissolved in 270 ml PBS] per well. Absorbance readings were obtained at 490 nm in a Bio-Tek plate reader.

#### *EGFR inhibitor studies*

Control MCF7 cells were serum-starved overnight and treated with the EGFR kinase inhibitor AG1478 (conc. in DMSO) or vehicle for 5 min. prior to the addition of 14 nM EGF or 5 nM IGF-I. After 5 min. of growth factor treatment, cell lysates were prepared and analyzed for ERK and Akt/PKB activation as described above.

#### **EXAMPLE 2**

(Herstatin, and its intron-encoded receptor-binding domain, were shown to bind specifically to IGF-1R with high (*e.g.*, nm) binding affinity)

The interaction of the receptor binding domain (RBD, encoded by HER-2 intron 8; int8 peptide) of herstatin with IGF-1R in transfected 3T3 cells was investigated. According to particular embodiments of the present invention, both full-length herstatin and its RBD bind specifically to IGF-1R with high binding affinity (*e.g.*, nm), and IGF-IR was thus shown herein to be a target of herstatin.

*Methods.* Cell lines, expression vectors, protein purification, pull down assays, antibodies, Western blot analysis and ELISA assays were as described under EXAMPLE 1, herein above.

*Results.* Figure 1A demonstrates that the Int8 peptide, purified from bacteria and immobilized on Protein S Sepharose™ 'pulled down' IGF-IR from 3T3 cell extracts, whereas Protein S Sepharose™ without peptide, or with an irrelevant peptide did not interact with IGF-IR.

Saturation binding of bacterial peptide Int8 to IGF-IR transfected 3T3 cells, and for comparison to parental 3T3 cells, was performed to determine the binding affinity of the Int8

peptide to IGF-1R. Figure 1B shows saturable binding by the RBD Int8 polypeptide that is specific for IGF-1R. The  $K_d$  for binding, determined from this and other saturation binding curves was found to be in the nM range (e.g., in the 40 to 150 nM range), which is comparable to the binding affinity of Int8 peptide to HER-2 (Doherty et al., *Supra*) and to EGFR.

5       The interaction between full-length herstatin and IGF-1R was also investigated. Figure 1C shows that herstatin, purified from transfected S2 insect cells, exhibited dose-dependent binding to IGF-1R at nM concentrations.

Figure 1D shows that full-length herstatin exhibited saturation binding to IGF-1R 3T3 cells, demonstrating nM binding affinity.

10       These results demonstrate that herstatin and its receptor binding domain bind specifically to IGF-1R with nM binding affinity (e.g., in the 40 to 150 nM range) and that IGF-1R is a target receptor of herstatin.

### EXAMPLE 3

15       (Herstatin was shown to prevent activation  
of IGF-1R by IGF-1 in MCF7 cells)

According to particular embodiments of the present invention, herstatin blocks activation of IGF-1R by IGF-1 (FIGURES 2A, 2B), and causes IGF-1R down-regulation (FIGURE 2A, lower portion).

20       *Methods.* Cell lines, expression vectors, protein purification, pull down assays, antibodies, Western blot analysis and ELISA assays were as described under EXAMPLE I, herein above. IGF-I was added either to MCF-7 breast carcinoma cells, or to an MCF-7/herstatin cell line stably transfected with herstatin, to determine whether herstatin expression affects activation of the IGF-1R by its ligand. MCF7 and MCF7/Hst cells were serum-starved  
25       overnight, treated with 5 nM IGF-I over a 60-minute timecourse, and harvested in NP-40 lysis buffer. 1mg of cell lysate was immunoprecipiated with IGF-1R $\beta$  antibody and protein A agarose beads. Immunoprecipitates were separated on a 10% SDS-PAGE gel and analyzed for IGF-1R expression and tyrosine phosphorylation. Western blots were scanned and quantified by densitometry.

30       *Results.* As expected, there is a robust IGF-I-mediated activation of the IGF-1R in MCF7



cells, demonstrated by enhanced tyrosine phosphorylated IGF-IR by 5 min (FIGURE 2A, left panel). In contrast, activation of the IGF-IR by IGF (revealed by receptor tyrosine phosphorylation) was blocked in the herstatin -expressing MCF7 cells (FIGURE 2A, right panel).

5 These results demonstrate that herstatin modulates IGF-IR-mediated signaling.

Additionally, as shown in FIGURE 2A (lower portion), herstatin not only prevents activation of IGF-IR by IGF-1 in MCF-7 cells (upper panels), but also caused down-regulation of IGF-1R (lower panels). Likewise, herstatin-transfected MCF-7 cells show decreased expression of IRS-2 expression (also important in cell survival) when compared to non-  
10 transfected MCF-7 cells (FIGURE 9).

#### EXAMPLE 4

(The herstatin RBD Int8 polypeptide bound in a specific, dose-dependent manner to EGFR, HER-2, HER-3, HER-4, IGF-1R and ΔEGFR, but did not bind to a mutant form of HER-3, FGFR-3, nor mock-transfected cells)  
15

The binding of the intron 8-encoded RBD, expressed as a bacterial peptide (Int8) was investigated to identify other receptor targets of herstatin. The herstatin RBD Int8 polypeptide bound in a specific, dose-dependent manner to EGFR, HER-2, HER-3, HER-4, IGF-1R and ΔEGFR, but did not bind to a mutant form of HER-3, FGFR-3, or mock-transfected cells  
20 (FIGURES 3A and 3B).

*Methods.* Cell lines, expression vectors, protein purification, pull down assays, antibodies and ELISA assays were as described under EXAMPLE 1, herein above. Briefly, Protein S Sepharose™ with or without immobilized Int 8 peptide, was incubated with extracts from Cos 7 cells transiently transfected with several different receptors (or, in the case of IGF-1  
25 with extracts from hIGFR-1-3T3 cells). Following washing steps, the protein bound to the agarose was analyzed as a Western blot with receptor-specific antibodies.

*Results.* As previously observed (Doherty et al., *Supra.*; Azios, *Supra*) EGFR and HER-2 from the transfected cell extracts bound specifically to the agarose with Int8 polypeptide (FIGURE 3A). In particular assays, an Int8 peptide with the Arg to Ile mutation at residue 31  
30 was somewhat less efficient in pulling-down the HER-2 receptor from the extracts (on average this herstatin variant appeared to bind about 2-fold less well than the comparable wild type

sequence (SEQ ID NO:24)).

FIGURE 3A also demonstrates that  $\Delta$ EGFR, a tumor variant of the EGFR missing its N-terminal subdomains I and II (Nishikawa et al., *Proc. Natl. Acad. Sci. USA* 91:7727-31, 1994) specifically associated with Int8 polypeptide.

5 An additional member of the erbB family, HER-4, was also 'pulled-down' by Int8 agarose.

High-affinity binding by Int8 polypeptide to endogenous HER-3 in MCF7 breast cancer cells was observed, independent of ligand activation (FIGURE 4B). Additionally, binding of the RBD Int8 polypeptide to purified (wild-type) HER-3 ectodomain expressed in stably transfected  
10 CHO cells was observed (FIGURE 4C).

However, in the case of one particular form of HER-3 (corresponding to the product of the HER-3 expression vector, a gift from Dr. Tracy Ram, Washington State University in Pullman) there was no detectable association of the expressed HER-3 with Int8 polypeptide agarose, despite abundant expression in the respective transfected cells (FIGURE 3A, third panel  
15 from top; and FIGURE 4A). Applicants have determined that this non-Int8 binding form of HER-3 has a single point mutation resulting in substitution of Glu for Gly (relative to accession no.: NM\_001982, nucleotide # 1877, and amino acid residue position 560) in the ectodomain of HER-3.

As disclosed in EXAMPLE 2 above with respect to the interaction of the Int8  
20 polypeptide with the IGF-1R, specific 'pull-down' of the  $\beta$  subunit of the IGF-1R from transfected cell extracts was observed (FIGURE 3A, bottom panel). This result may reflect the fact that the IGF-1R contains regions of ectodomain sequence homology with the EGFR (Garrett et al., *Cell* 110:763-73, 2002).

The FGFR-3, a receptor tyrosine kinase with Ig-like motifs and no structural homology  
25 with the ErbB family ectodomains, did not bind to the Int8 peptide (FIGURE 3A).

Therefore, according to particular aspects of the present invention, the herstatin RBD Int8 polypeptide binds in a high-affinity, specific manner to EGFR, HER-2, HER-3. HER-4, IGF-1R and  $\Delta$ EGFR, but does not bind to a mutant form of HER-3 (single point mutation resulting in substitution of Glu for Gly at amino acid position 560), to FGFR-3, or to mock-

transfected cells.

*ELISA assay results.* ELISA analysis used to quantify bound RBD Int8 polypeptide to further examine interaction of the int8 polypeptide with the extracellular domain of the various receptors at the cell surface. As was shown for the IGF-1R (hIGF-1R-3T3 cells) in EXAMPLE 1 above, FIGURE 3B shows that the Int8 polypeptide bound in a specific and dose-dependent manner to EGFR, HER-2, HER-4, and  $\Delta$ EGFR, but not to a mutant form of HER-3, FGFR-3, or mock-transfected Cos-7 cells, in agreement with results obtained by the 'pull-down' assays FIGURE 3A).

Binding affinities were further characterized by generating saturation-binding curves (FIGURES 5A and 5B). The RBD Int8 polypeptide bound with high affinity to HER-2-transfected Cos-7 cells (in particular assays,  $K_D = 50 \pm 6$  nM; FIGURE 5A, open squares; among various assays, in the 40 to 150 nM range) and to EGFR-transfected Cos-7 cells (in particular  $K_D = 78 \pm 10$  nM; FIGURE 5A, filled squares; among various assays in the 40 to 150 nM range) with binding affinities, assessed by comparative nonlinear regression analysis, that were not significantly different ( $P=0.40$ ) (FIGURE 5A). Furthermore, similar to the determination of EXAMPLE 2 above ( $K_D = 40$  nM in particular assays; among various assays in the 40 to 150 nM range), the RBD Int8 polypeptide bound to the IGF-IR/3T3 cells with an affinity ( $K_D = 70 \pm 21$  in particular assays; among various assays in the 40 to 150 nM range) that was not significantly different ( $P=0.96$ ) from the affinity for HER-2/3T3 cells ( $K_D = 66 \pm 16$ ) (FIGURE 5B) (among various assays in the 40 to 150 nM range).

In particular assays, the mutant Int8 polypeptide with Arg31Ile bound somewhat less well (perhaps 2-fold) to the HER-2 receptor overexpressing cells, even though the herstatin ELISA detected the wildtype and mutant peptide equally.

These results show, therefore, that the RBD Int8 polypeptide bound to EGFR, HER-2, and IGF-1R with similar (overlapping) binding affinities.

#### EXAMPLE 5

(Relative binding of herstatin between 3T3/HER-2 and 3T3/IGF-IR cells, and between 3T3/HER-2 and Cos-7/EGF cells was directly compared, and the relative affinities of herstatin and RGB Int8 polypeptide were determined on 3T3/HER-2 cells)

ELISA analysis was performed to compare relative binding of herstatin between 3T3/HER-2 and 3T3/IGF-IR cells, and between 3T3/HER-2 and Cos-7/EGF cells. Additionally, the relative affinities of herstatin and RGB Int8 polypeptide were determined on 3T3/HER-2 cells.

5       *Methods.* Cell lines, expression vectors, protein purification, antibodies and ELISA assays were as described under EXAMPLE 1, herein above.

*Results.* A direct comparison of the binding of herstatin to 3T3/HER-2 and 3T3/IGF-IR cells revealed that the affinity for the IGF-1R ( $K_D \sim 151$  nM) was lower ( $P < .0001$ ) by about 10-fold (FIGURE 6A). The full-length herstatin bound to 3T3/HER-2 cells with a  $K_D = 14.7 \pm 1.8$  nM, which is greater than the binding affinity of RBD Int8 polypeptide ( $P < .0001$ ) by 3-4 fold (FIGURE 6A).

      The dissociation constant of FIGURE 6A for EGFR was similar to that of HER-2, and was unaffected by ligand occupation indicated by a  $K_D = 16.4 \pm 3.6$  nM versus  $16.3 \pm 3.6$  nM (respectively) for Cos-7/EGFR treated or not with 10 nM EGF (FIGURE 6B).

15

#### EXAMPLE 6

(Herstatin exhibited saturation binding to endogenous receptors in A431 epidermoid carcinoma cells)

20       Herstatin binding to endogenous receptors in A431 epidermoid carcinoma cells was investigated to determine if a one-affinity site binding model was the best fit for EGFR-specific binding of herstatin, in the presence and absence of EGF.

*Methods.* A431 cells were from ATCC.

25       *Results.* Herstatin exhibited saturation binding to endogenous receptors in A431 epidermoid carcinoma cells, which express very high levels of EGFR and low levels of other ErbB receptors (FIGURE 6C). At saturation,  $6.9 \pm 0.4$  pmol of herstatin were bound indicating about  $2 \times 10^6$  binding sites/cell, which matches the number of EGFR per A431 cell at  $2 \times 10^6$  (Filmus et al., *Biochem. Biophys. Res. Commun.*, 131:207-15, 1985; Filmus et al., *Biochem. Biophys. Res. Commun.* 128:898-905, 1985). Comparison of nonlinear models indicated that a hyperbolic one-affinity site binding model was the best fit for EGFR-specific binding of  
30       herstatin, in the presence and absence of EGF.

**EXAMPLE 7**

(Herstatin effects were shown to be receptor specific)

Because herstatin binds to multiple receptors, binding studies were performed to demonstrate that the effects of herstatin are receptor-specific.

*Methods.* Cells and western blot analysis were as described under EXAMPLE 1 above.

*Results.* As demonstrated herein above, herstatin does not bind to the FGFR. FIGURE 7A (upper panel) and FIGURE 7D show that herstatin blocks intracellular signaling (MAPK phosphorylation) by Heregulin (the ligand for HER-3 and HER-4) and EGF (the ligand for the EGFR), respectively, in MCF-7 cells, whereas herstatin does not affect FGF signaling (MAPK phosphorylation) in MCF-7 cells (FIGURE 7A, lower panel), and does not inhibit IGF-1-mediated ERK phosphorylation in MCF-7 cells (FIGURE 7B).

Additionally, FIGURE 7C shows that herstatin down-regulates HER-1, HER-3 and HER-4 receptors in MCF-7 cells.

**EXAMPLE 8**

(Herstatin inhibited Heregulin/HER-4-mediated activation of, and IGF-1/IGF1R-mediated activation of the PI3/Akt pathway that is important in cell survival)

The physiological effects of herstatin on HER-4-mediated signaling were investigated. The protein kinase called Akt is a key regulator of cellular survival. Activation of Akt is both necessary and sufficient for survival of cells. Stimulation of activated Akt causes inappropriate cell survival, or prevents normal cell death, which has been found to occur in several human cancers. HER-2 and the EGF receptor, for example, both cause activation of the Akt survival signal whereby, according to current theory and belief, they cause oncogenic growth (Blumenfeld & Hunter, *Nature* 411:355-365, 2001; Datta et al., *Genes and Development* 13:2905-2907, 2000; and Yarden & Slikowski, *Nature Reviews, Molecular Cell Biology*, 2:127-137).

*Methods. Measurement of activated phospho-akt (activated AKT) in EGFR3T3 cells.* Measurement of activated AKT (phospho-akt) was accomplished using standard Western blotting techniques, employing a commercially available anti-phospho-akt antibody (Santa Cruz). Briefly, CHO cells were transfected with HER-4 alone, or cotransfected with HER-4 and herstatin. Twenty-four (24) hours after transfection, serum-starved cells were treated with

heregulin or vehicle for 15 and 30 min. The cells were extracted and analyzed as a Western blot with antibodies specific for activated Akt (anti-phospho-Akt), or for total Akt.

*Results.* Heregulin caused a robust increase in phospho-Akt in the absence of herstatin, whereas heregulin induction of phosphoAkt was reduced in herstatin expressing cells.

5        Additionally, as shown in FIGURE 8, herstatin inhibited IGF-1/IGF-1R-mediated activation of the PI3/Akt pathway.

         Furthermore, FIGURE 9 shows the effect of herstatin -expression on the expression levels of various signaling proteins. Herstatin expression in MCF7 breast carcinoma cells down-regulated IGF-1R, IRS-1, IRS-2 (also important in cell survival), and pKB/Akt expression, but  
10    MAPK expression was unaffected. Herstatin expression also induced expression of the p66 isoform of Shc, which is not detectable by Western Blot in parental MCF7 cells.

         Therefore, according to particular aspects of the present invention, herstatin inhibits activation of the PI3/Akt and IRS-2 pathways that are important in cell survival.

15

#### **EXAMPLE 9** (Herstatin inhibited IGF-1-mediated survival of MCF7 cells)

         Previous studies have shown that stable expression of herstatin in MCF7 breast carcinoma cells resulted in diminished heregulin-stimulated proliferation (Jhabvala-Romero et al., *Oncogene* 22:8178-86, 2003). To further investigate the effect of herstatin on IGF-I action,  
20    the IGF-I-induced growth of parental MCF7 cells and two clones stably transfected with herstatin (MCF7/Hst#1 and MCF7/Hst#2) was investigated.

*Methods.* MCF7 parental and MCF7/Hst breast cancer cells, stably transfected with herstatin (either MCF7/Hst#1, a low-level herstatin -expressing clone, or MCF7/Hst#2, a relatively high-level herstatin -expressing clone), were plated into 24-well plates at 40,000 cells  
25    per well overnight and the MTS assay was conducted in triplicate wells to quantify viable cells at time zero. The cells were then treated in serum-free media with vehicle or with 10 nM IGF-I and triplicate wells were quantified by the MTS assay on day 1, 2 and 3. The results are plotted as mean percent of the start at zero time. The error bars represent the standard error of the mean.

*Results.* FIGURE 10A and 10B show that herstatin expression blocks IGF-1-mediated  
30    survival of MCF7 cells. Parental MCF7 cells grew in response to IGF-I, whereas cell viability

decreased in the absence of growth factor. Both of the MCF7/Hst clones, however, failed to exhibit IGF-I-stimulated growth. Furthermore, the growth reduction occurred faster in clone #1, which expresses relatively more herstatin, indicating that herstatin affects IGF-I-mediated growth in a concentration-dependent manner.

5

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## CLAIMS

1. A method for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising administering to a subject in need thereof, a therapeutically effective amount of a herstatin, or of a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell of the subject, wherein the at least one target receptor is selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

2. The method of claim 1, wherein the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, including the C-terminal 79 contiguous amino acids of SEQ ID NO:2.

3. The method of claims 1 or 2, wherein the herstatin, or variant thereof, comprises SEQ ID NO:23.

4. The method of claims 1 or 2, wherein the herstatin, or variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ .

5. A method for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising administering to a subject in need thereof, a therapeutically effective amount of an Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell of the subject, wherein the at least one target receptor is selected from the group consisting of:  $\square$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

6. The method of claim 5, wherein the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

7. The method of claim 5 or 6, wherein the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

8. The method of claims 5 or 6, wherein the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity



binding constant of at least  $10^7 \text{ M}^{-1}$ .

9. The method of any of claims 1-8, wherein the condition is a cellular proliferative condition or disorder.

10. The method of any of claims 1-9, wherein the condition is cancer.

5 11. The method of claim 10, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, colon, lung cancer, glioblastoma ovarian cancer, pancreatic cancer and prostate cancer.

12. The method of any of claims 1-11, wherein the target cell does not express EGFR (HER-1, erbB-1) or HER-2 (erbB-2), or does not express either.

10 13. The method of claims 10 or 11, wherein the cancer is refractory, at least to some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different from herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants.

15 14. The method of claim 13, wherein the cancer is breast cancer, or prostate cancer.

15. The method of claim 13, wherein the at least one other agent comprises a receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

16. The method of any of claims 1-15, further comprising administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular  
20 domain of a cellular receptor of the target cell.

17. The method of claim 16, wherein the receptor-specific antibody binds to a cellular receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

18. The method of claim 17, wherein the receptor-specific antibody is the HER-2-  
25 specific antibody rhuMAb4D5.

19. The method of claim 16, wherein the receptor-specific antibody binds to a cellular receptor of the target cell that is different from the at least one cellular receptor bound by the Herstatin, or the variant thereof.

20. The method of any of claims 1-19, further comprising administration of a

therapeutically effective amount of a chemotherapeutic agent.

21. The method of claim 20, wherein the chemotherapeutic agent is an anti-neoplastic agent selected from the group consisting of: cyclophosphamide, triethylenephosphoramidate, triethylenethiophosphoramidate, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedapa, uredapa, aminoglutethimide, L-asparaginase, BCNU, benzodapa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin, estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

22. A method for conferring to a therapeutic agent the capacity to be targeted to a target cell, wherein the target cell is characterized by expression of at least one target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, comprising attaching the therapeutic agent to herstatin, or to a variant thereof, that binds to the extracellular domain of the at least one target receptor.

23. The method of claim 22, wherein the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, including the C-terminal 79 contiguous amino acids of SEQ ID NO:2

24. The method of claims 22 or 23, wherein the herstatin, or variant thereof, comprises SEQ ID NO:23.

25. The method of claims 22 or 23, wherein the herstatin, or variant thereof binds to the extracellular domain of the at least one target receptor with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ .

26. A method for targeting a therapeutic agent to target cells, comprising attaching the therapeutic agent to an Int8 RBD polypeptide, or to a variant thereof, that binds to the extracellular domain of at least one target receptor of a target cell being targeted, wherein the at

least one target receptor is selected from the group consisting of: □EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

27. The method of claim 26, wherein the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of  
5 SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

28. The method of claim 26 or 27, wherein the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

29. The method of claims 26 or 27, wherein the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity  
10 binding constant of at least  $10^7 \text{ M}^{-1}$ .

30. The method of any of claims 22-29, wherein the target cell is a cancer cell.

31. The method of claim 30, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, colon, lung cancer, glioblastoma ovarian cancer, pancreatic cancer and prostate cancer.

15 32. The method of any of claims 22-31, wherein the target cell does not express EGFR (HER-1, erbB-1) or HER-2 (erbB-2), or does not express either.

33. A pharmaceutical composition for treating a condition characterized by altered cellular receptor expression or receptor-mediated signaling, comprising, along with a pharmaceutically acceptable carrier or excipient, a first agent selected from the group consisting  
20 of: herstatin, or a variant thereof; a Int8 RBD polypeptide, or a variant thereof; and combinations thereof, the composition further comprising a second agent selected from the group consisting of: a receptor-specific antibody that binds to the extracellular domain (ECD) of a cellular receptor of the target cell; a small molecule receptor tyrosine kinase inhibitor; and combinations thereof, with the proviso that the receptor-specific antibody is not a HER-1 (EGFR) or HER-2-  
25 specific antibody.

34. The composition of claim 33, wherein the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, including the C-terminal 79 contiguous amino acids of SEQ ID NO:2.

35. The composition of claims 33 or 34, wherein the herstatin, or variant thereof, comprises SEQ ID NO:23.

36. The composition of claims 33, wherein the Int8 RBD polypeptide, or a variant thereof comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a  
5 fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

37. The composition of claim 33 or 36, wherein the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

38. The composition of any of claims 33-37, wherein the receptor-specific antibody binds to a cellular receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3);  
10 HER-4 (erbB-4) and IGF-1.

39. The composition of claim 38, wherein the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5.

40. Use of a herstatin, or of a variant thereof, that binds to the extracellular domain of at least one target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3);  
15 HER-4 (erbB-4) and IGF-1, for the manufacture of a medicament for treating a condition characterized by altered expression of, or altered intracellular signaling mediated by the at least one target receptor.

41. The use of claim 40, wherein the herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2  
20 of about 80 to 419 contiguous residues in length, including the C-terminal 79 contiguous amino acids of SEQ ID NO:2

42. The use of claims 40 or 41, wherein the herstatin, or variant thereof, comprises SEQ ID NO:23.

43. The use of claims 40 or 41, wherein the herstatin, or variant thereof binds to the  
25 extracellular domain of the at least one target receptor with an affinity binding constant of at least  $10^7 \text{ M}^{-1}$ .

44. Use of a Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of at least one target receptor selected from the group consisting of:  $\Delta$ EGFR; HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, for the manufacture of a medicament for treating a

condition characterized by altered expression of, or altered intracellular signaling mediated by the at least one target receptor.

45. The use of claim 44, wherein the Int8 RBD polypeptide, or a variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of  
5 SEQ ID NO:1 of about 50 to 79 contiguous residues in length.

46. The use of claim 44 or 45, wherein the Int8 RBD polypeptide, or variant thereof, comprises SEQ ID NO:24.

47. The use of claims 44 or 45, wherein the Int8 RBD polypeptide, or a variant thereof binds to the extracellular domain of the at least one target receptor with an affinity  
10 binding constant of at least  $10^7 \text{ M}^{-1}$ .

48. The use of any of claims 40-47, wherein the condition is a cellular proliferative condition or disorder.

49. The use of any of claims 40-48, wherein the condition is cancer.

50. The use of any of claims 40-49, wherein the target cell does not express EGFR  
15 (HER-1, erbB-1) or HER-2 (erbB-2), or does not express either.

51. The method of claim 50, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, colon, lung cancer, glioblastoma ovarian cancer, pancreatic cancer and prostate cancer.

52. The use of any one of claims 49-51, wherein the cancer is refractory, at least to  
20 some extent, to treatment by at least one other therapeutic agent that is specific for a receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1, and wherein the at least one other therapeutic agent is different from herstatin, herstatin variants, int8 RDB polypeptides, and int8 RDB polypeptide variants.

25 53. The use of claim 52, wherein the cancer is breast cancer or prostate cancer.

54. The use of claim 52, wherein the at least one other agent comprises a receptor-specific antibody, or a small-molecule receptor tyrosine kinase inhibitor.

55. The use of claim 54, wherein the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5.

56. The use of any of claims 40-53, further comprising administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular domain of a cellular receptor of the target cell.

57. The use of claim 56, wherein the receptor-specific antibody binds to a cellular  
5 receptor selected from the group consisting of: EGFR (HER-1, erbB-1);  $\Delta$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4) and IGF-1.

58. The use of claim 57, wherein the receptor-specific antibody is the HER-2-specific antibody rhuMAb4D5.

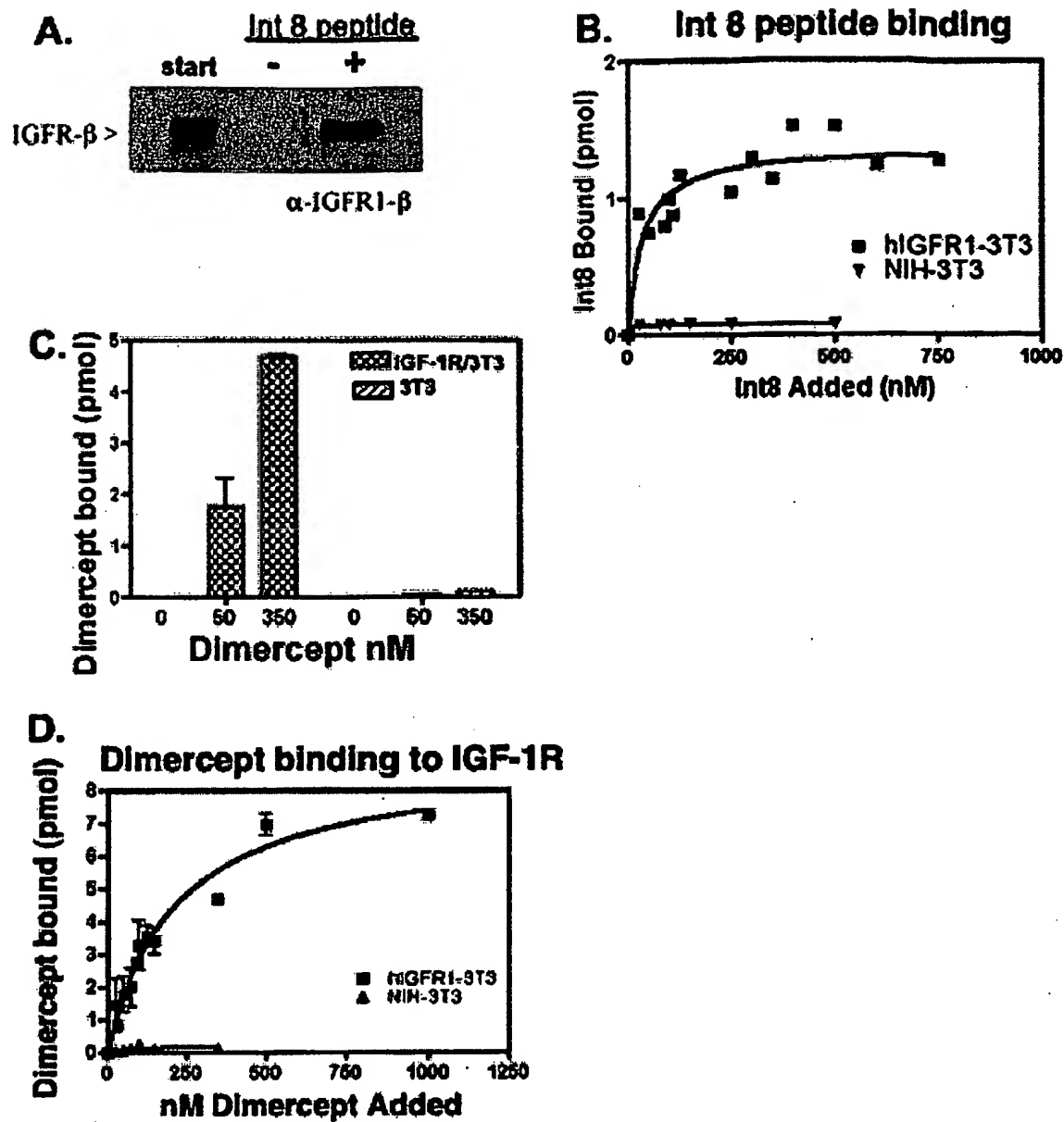
59. The use of claim 56, wherein the receptor-specific antibody binds to a cellular  
10 receptor of the target cell that is different from the at least one cellular receptor bound by the Herstatin, or the variant thereof.

60. The use of any of claims 40-59, further comprising administration of a therapeutically effective amount of a chemotherapeutic agent.

61. The use of claim 60, wherein the chemotherapeutic agent is an anti-neoplastic  
15 agent selected from the group consisting of: cyclophosphamide, triethylenephosphoramidate, triethylenethiophosphoramidate, flutamide, altretamine, triethylenemelamine, trimethylolmelamine, meturedapa, uredapa, aminoglutethimide, L-asparaginase, BCNU, benzodepa, bleomycin, busulfan, camptothecin, capecitabine, carboquone, chlorambucil, cytarabine, dactinomycin, daunomycin, daunorubicin, docetaxol, doxorubicin, epirubicin,  
20 estramustine, dacarbazine, etoposide, fluorouracil, gemcitabine, hydroxyurea, ifosfamide, improsulfan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, novembrichin, paclitaxel, piposulfan, plicamycin, prednimustine, procarbazine, tamoxifen, temozolomide, teniposide, thioguanine, thiotepa, UFT, uracil mustard, vinblastine, vincristine, vinorelbine and vindesine.

25 62. A method for identification of cells having HER-3 receptors that do not bind herstatin, int 8 RDB polypeptides, or variants thereof, comprising: obtaining a cellular sample; and determining, using one or more suitable assays, whether the cells express SEQ ID NO:14, wherein cells having HER-3 receptors that do not bind herstatin are identified if SEQ ID NO:14 is expressed.

63. A method for screening for cells that are, at least to some extent, non-responsive to herstatin, int 8 RDB polypeptides, or variants thereof, comprising obtaining a cellular sample; and determining, using one or more suitable assays, whether the cells express SEQ ID NO:14, wherein the cells are determined to be, at least to some extent, non-responsive to herstatin, int 8  
5 RDB polypeptides, or variants thereof, if the cells express SEQ ID NO:14.



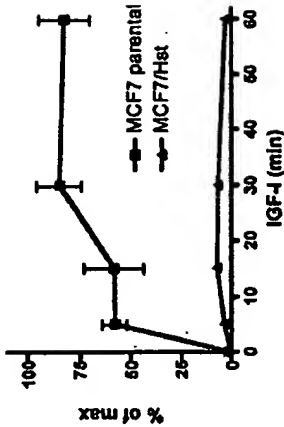
FIGURES 1A, 1B, 1C and 1D



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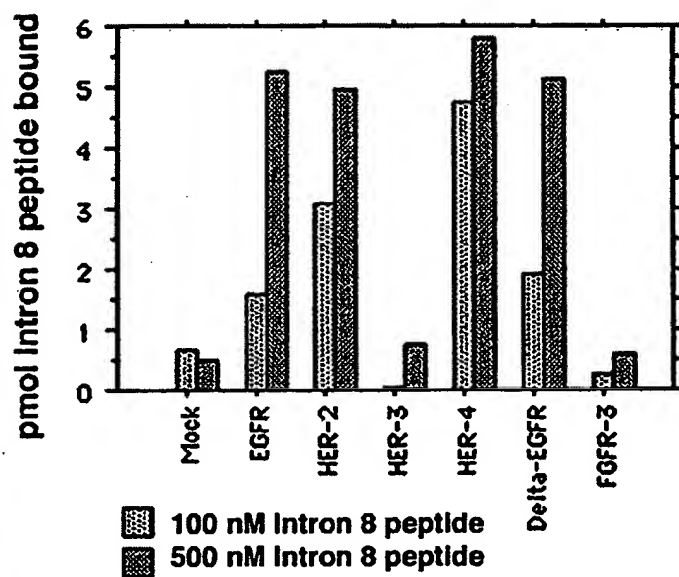
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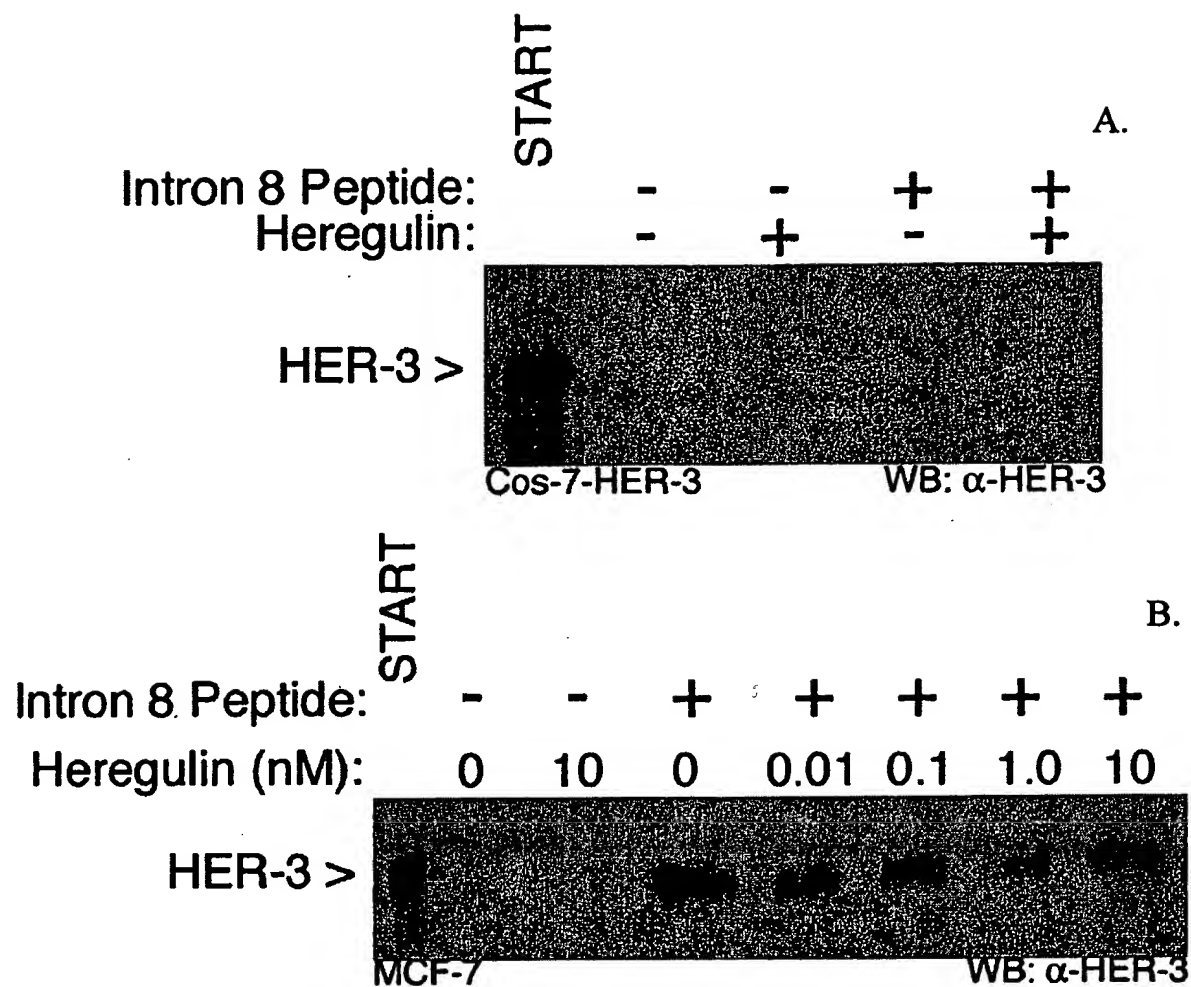
Figures 2A and 2B



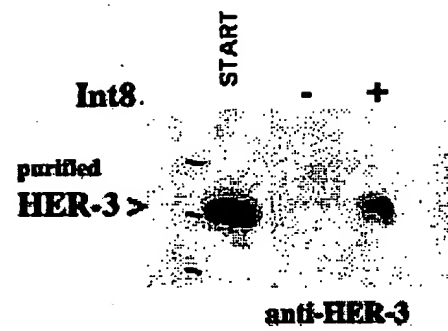
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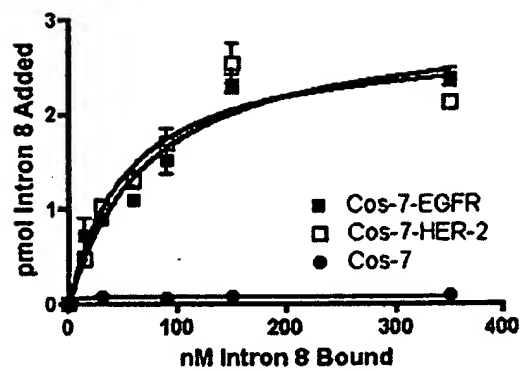
**FIGURES 3A, and 3B**



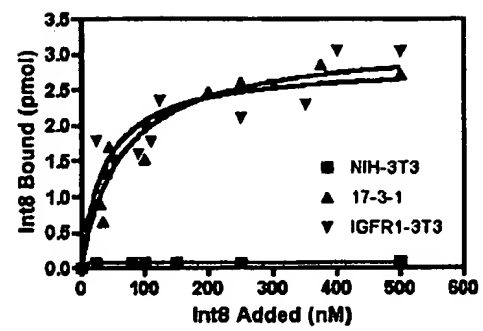
FIGURES 4A and 4B

**FIGURE 4C**

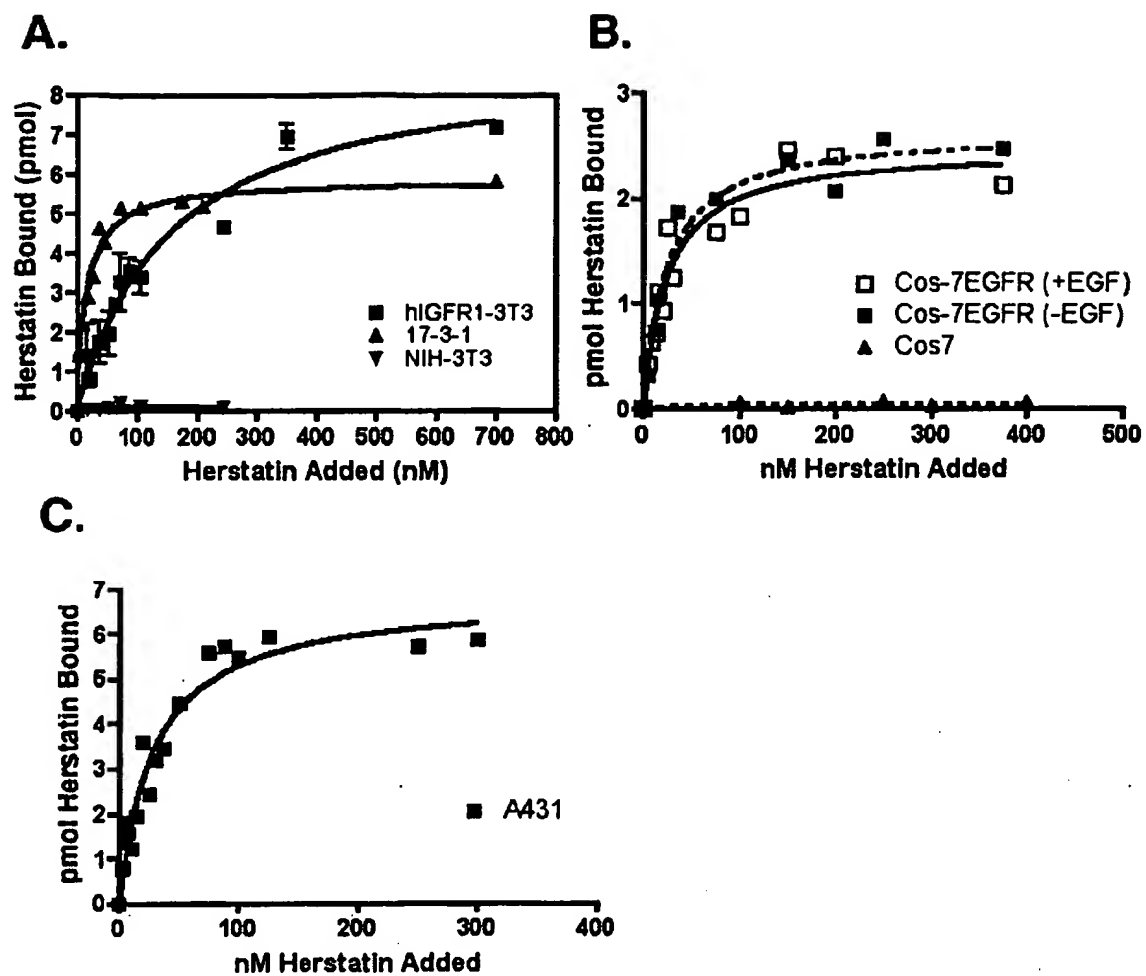
A



B.



FIGURES 5A and 5B



FIGURES 6A, 6B and 6C

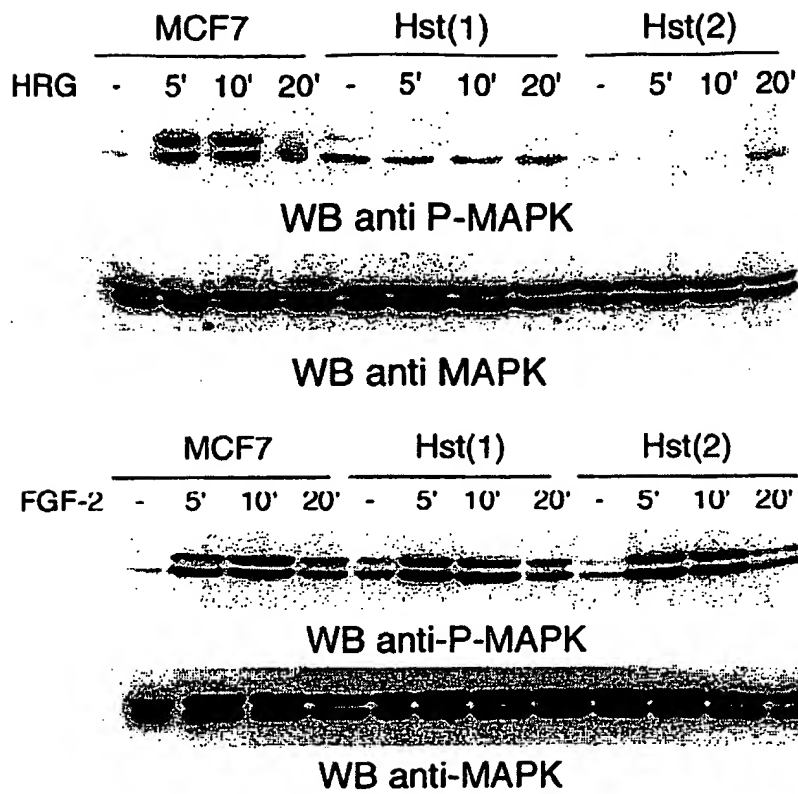


FIGURE 7A

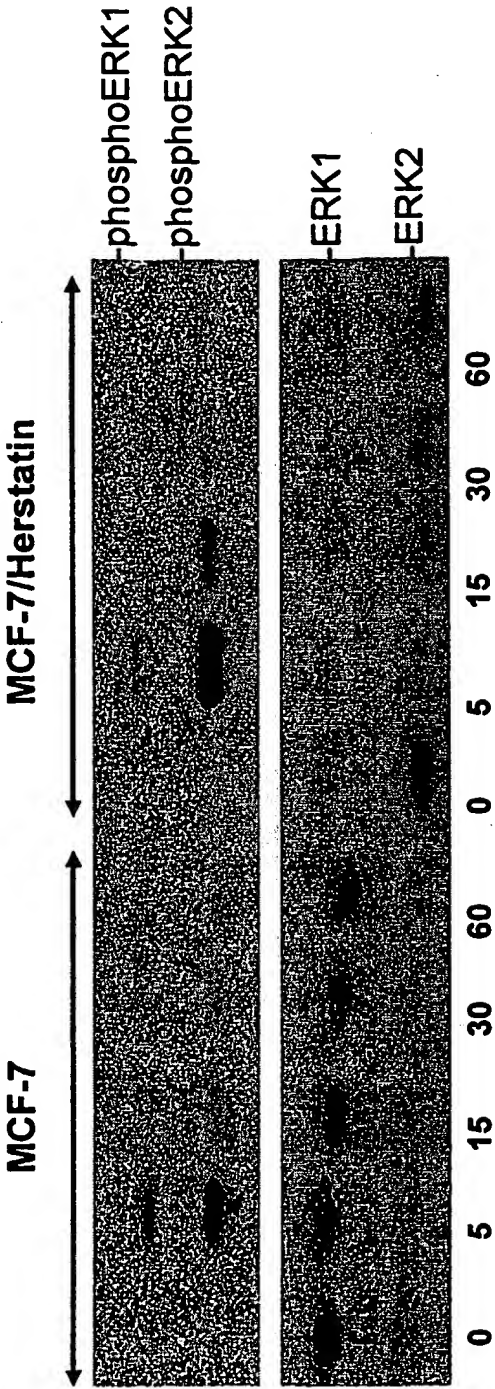
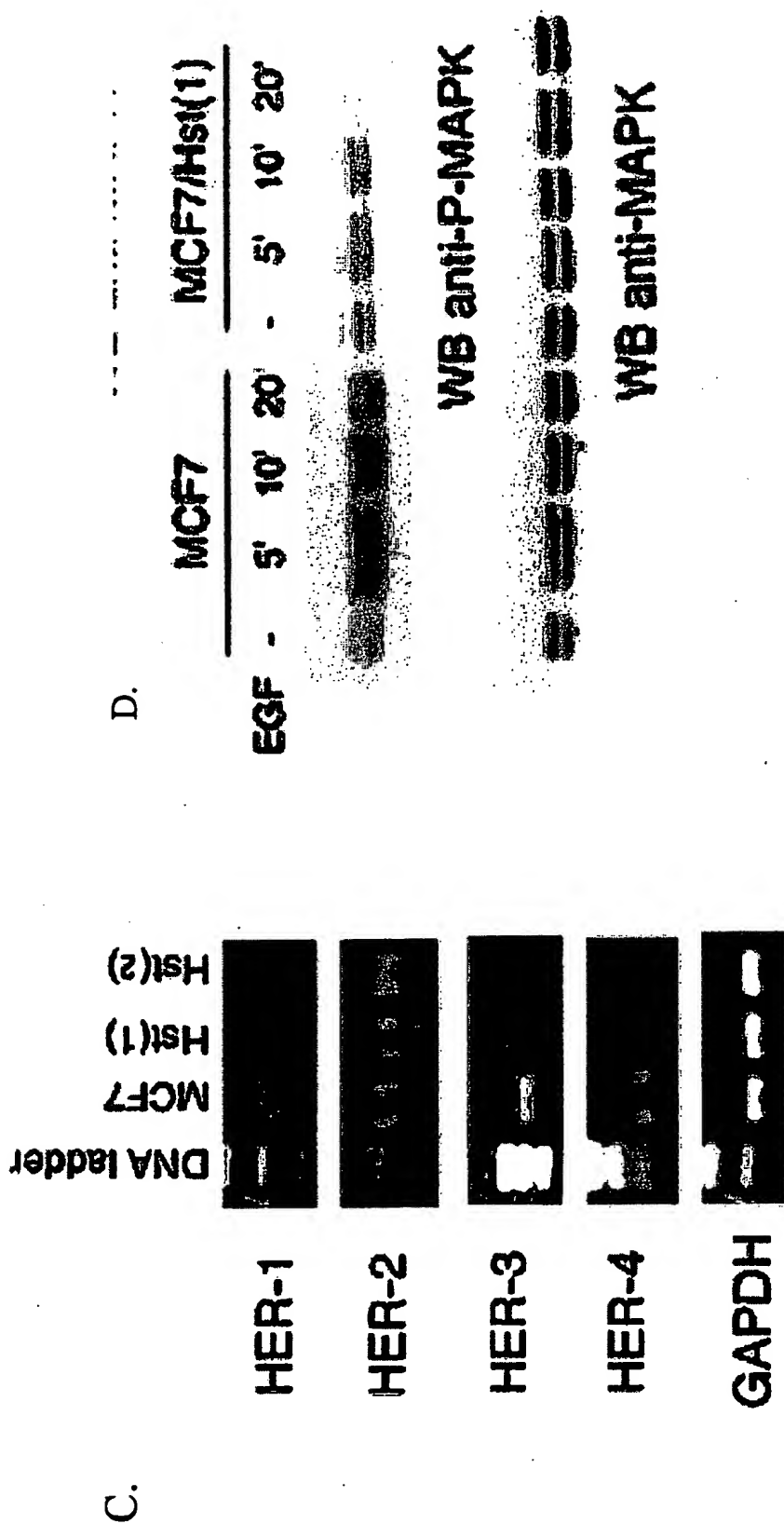
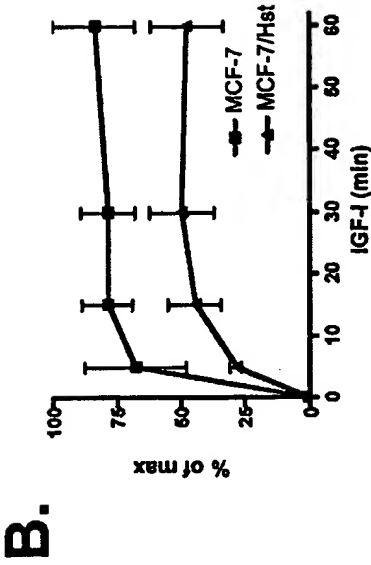
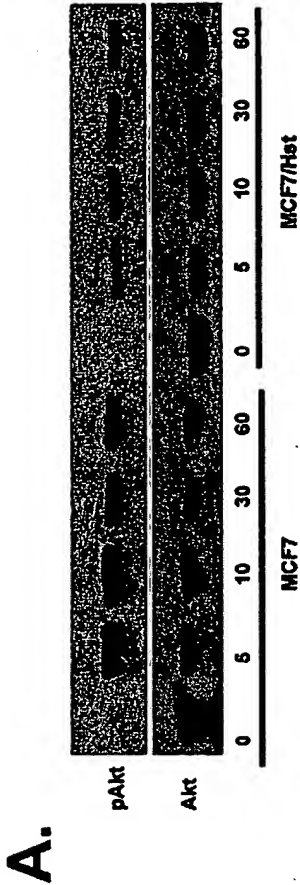


FIGURE 7B

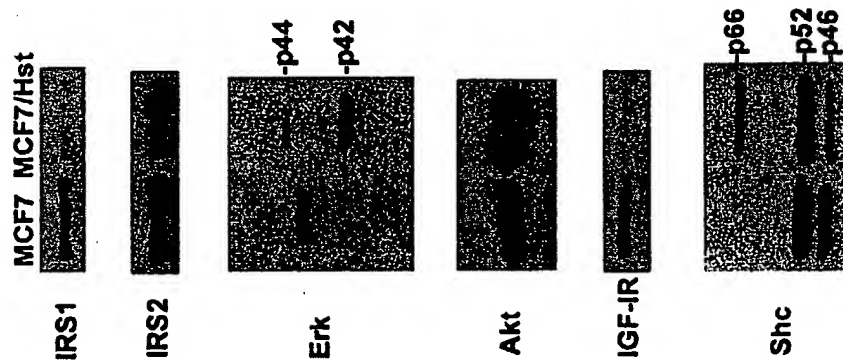


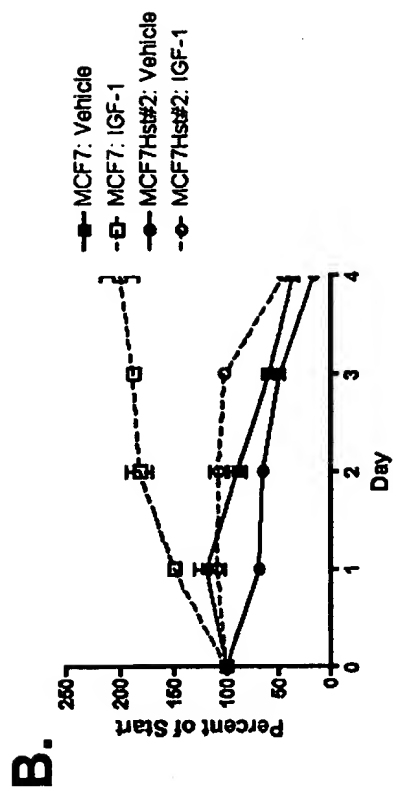
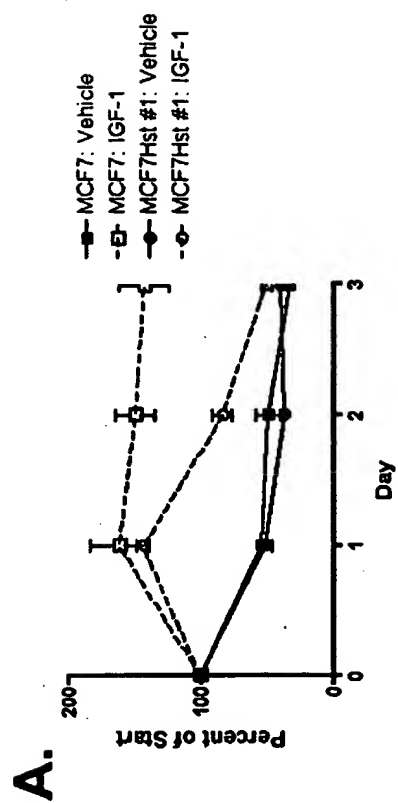


FIGURES 7C and 7D



Figures 8A and 8B

**Figure 9**



Figures 10A and 10B

## SEQUENCE LISTING

<110> OREGON HEALTH & SCIENCE UNIVERSITY  
Clinton, Gail M.  
Shamieh, Lara

<120> COMPOSITIONS AND METHODS FOR MODULATING SIGNALING BY IGF-1  
RECEPTOR AND ERBB RECEPTORS

<130> 49321-137

<150> US 60/590,473  
<151> 2004-07-23

<150> US 60/564,893  
<151> 2004-04-22

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Ser Trp Asp Xaa Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45

Ser Pro Thr Ser Val Xaa Ile Ser Pro Val Ser Val Gly Arg Gly Xaa  
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Asp Pro Asp Ala His Val Ala Val Xaa Leu Ser Arg Tyr Glu Gly

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 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr  
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Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val  
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu  
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Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr  
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Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Arg Arg Thr Thr Pro  
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Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys  
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Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys  
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Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys  
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Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu  
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Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
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Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
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Phe Leu Xaa Pro Ser Trp Asp Xaa Val Ser Ala Phe Tyr Ser Leu Pro  
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## 49321-137.ST25.txt

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Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
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Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
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Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr  
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Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val  
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 aggccacctc gtcggcgtcc gcccgagtcc ccgcctcgcc gccaacgcca caaccaccgc 180  
 gcacggcccc ctgactccgt ccagtattga tcgggagagc cggagcgcgc tcttcgggga 240  
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 Leu Ala Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val  
 15 20 25 30  
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 Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp  
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 Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe  
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 Leu Lys Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn  
 80 85 90  
 aca gtg gag cga att cct ttg gaa aac ctg cag atc atc aga gga aat 576  
 Thr Val Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn  
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 Ala Asn Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu  
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160	170	
aac atg tcg atg gac ttc cag aac cac ctg ggc agc tgc caa aag tgt	816	
Asn Met Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys		
175	185	190
gat cca agc tgt ccc aat ggg agc tgc tgg ggt gca gga gag gag aac	864	
Asp Pro Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn		
195	200	205
tgc cag aaa ctg acc aaa atc atc tgt gcc cag cag tgc tcc ggg cgc	912	
Cys Gln Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg		
210	215	220
tgc cgt ggc aag tcc ccc agt gac tgc tgc cac aac cag tgt gct gca	960	
Cys Arg Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala		
225	230	235
ggc tgc aca ggc ccc cgg gag agc gac tgc ctg gtc tgc cgc aaa ttc	1008	
Gly Cys Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe		
240	245	250
cga gac gaa gcc acg tgc aag gac acc tgc ccc cca ctc atg ctc tac	1056	
Arg Asp Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr		
255	260	265
aac ccc acc acg tac cag atg gat gtg aac ccc gag ggc aaa tac agc	1104	
Asn Pro Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser		
275	280	285
ttt ggt gcc acc tgc gtg aag aag tgt ccc cgt aat tat gtg gtg aca	1152	
Phe Gly Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr		
290	295	300
gat cac ggc tcg tgc gtc cga gcc tgt ggg gcc gac agc tat gag atg	1200	
Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met		
305	310	315
gag gaa gac ggc gtc cgc aag tgt aag aag tgc gaa ggg cct tgc cgc	1248	
Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg		
320	325	330
aaa gtg tgt aac gga ata ggt att ggt gaa ttt aaa gac tca ctc tcc	1296	
Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser		
335	340	345
ata aat gct acg aat att aaa cac ttc aaa aac tgc acc tcc atc agt	1344	
Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser		
355	360	365
ggc gat ctc cac atc ctg ccg gtg gca ttt agg ggt gac tcc ttc aca	1392	
Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr		
370	375	380
cat act cct cct ctg gat cca cag gaa ctg gat att ctg aaa acc gta	1440	
His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val		
385	390	395

## 49321-137.ST25.txt

aag gaa atc aca ggg ttt ttg ctg att cag gct tgg cct gaa aac agg	1488
Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg	
400 405 410	
acg gac ctc cat gcc ttt gag aac cta gaa atc ata cgc ggc agg acc	1536
Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr	
415 420 425 430	
aag caa cat ggt cag ttt tct ctt gca gtc gtc agc ctg aac ata aca	1584
Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr	
435 440 445	
tcc ttg gga tta cgc tcc ctc aag gag ata agt gat gga gat gtg ata	1632
Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile	
450 455 460	
att tca gga aac aaa aat ttg tgc tat gca aat aca ata aac tgg aaa	1680
Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys	
465 470 475	
aaa ctg ttt ggg acc tcc ggt cag aaa acc aaa att ata agc aac aga	1728
Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg	
480 485 490	
ggt gaa aac agc tgc aag gcc aca ggc cag gtc tgc cat gcc ttg tgc	1776
Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys	
495 500 505 510	
tcc ccc gag ggc tgc tgg ggc ccg gag ccc agg gac tgc gtc tct tgc	1824
Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys	
515 520 525	
cgg aat gtc agc cga ggc agg gaa tgc gtg gac aag tgc aac ctt ctg	1872
Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu	
530 535 540	
gag ggt gag cca agg gag ttt gtg gag aac tct gag tgc ata cag tgc	1920
Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys	
545 550 555	
cac cca gag tgc ctg cct cag gcc atg aac atc acc tgc aca gga cgg	1968
His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg	
560 565 570	
gga cca gac aac tgt atc cag tgt gcc cac tac att gac ggc ccc cac	2016
Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His	
575 580 585 590	
tgc gtc aag acc tgc ccg gca gga gtc atg gga gaa aac aac acc ctg	2064
Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu	
595 600 605	
gtc tgg aag tac gca gac gcc ggc cat gtg tgc cac ctg tgc cat cca	2112
Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro	
610 615 620	
aac tgc acc tac gga tgc act ggg cca ggt ctt gaa ggc tgt cca acg	2160
Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr	

49321-137.ST25.txt

625	630	635	
aat ggg cct aag atc ccg tcc atc gcc act ggg atg gtg ggg gcc ctc Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu 640 645 650			2208
ctc ttg ctg ctg gtg gtg gcc ctg ggg atc ggc ctc ttc atg cga agg Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg 655 660 665 670			2256
cgc cac atc gtt cgg aag cgc acg ctg cgg agg ctg ctg cag gag agg Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg 675 680 685			2304
gag ctt gtg gag cct ctt aca ccc agt gga gaa gct ccc aac caa gct Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala 690 695 700			2352
ctc ttg agg atc ttg aag gaa act gaa ttc aaa aag atc aaa gtg ctg Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu 705 710 715			2400
ggc tcc ggt gcg ttc ggc acg gtg tat aag gga ctc tgg atc cca gaa Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu 720 725 730			2448
ggt gag aaa gtt aaa att ccc gtc gct atc aag gaa tta aga gaa gca Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala 735 740 745 750			2496
aca tct ccg aaa gcc aac aag gaa atc ctc gat gaa gcc tac gtg atg Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met 755 760 765			2544
gcc agc gtg gac aac ccc cac gtg tgc cgc ctg ctg ggc atc tgc ctc Ala Ser Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu 770 775 780			2592
acc tcc acc gtg cag ctc atc acg cag ctc atg ccc ttc ggc tgc ctc Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu 785 790 795			2640
ctg gac tat gtc cgg gaa cac aaa gac aat att ggc tcc cag tac ctg Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu 800 805 810			2688
ctc aac tgg tgt gtg cag atc gca aag ggc atg aac tac ttg gag gac Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp 815 820 825 830			2736
cgt cgc ttg gtg cac cgc gac ctg gca gcc agg aac gta ctg gtg aaa Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys 835 840 845			2784
aca ccg cag cat gtc aag atc aca gat ttt ggg ctg gcc aaa ctg ctg Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu 850 855 860			2832
ggt gcg gaa gag aaa gaa tac cat gca gaa gga ggc aaa gtg cct atc			2880



## 49321-137.ST25.txt

Gly	Ala	Glu	Glu	Lys	Glu	Tyr	His	Ala	Glu	Gly	Gly	Lys	Val	Pro	Ile		
	865						870					875					
aag	tgg	atg	gca	ttg	gaa	tca	att	tta	cac	aga	atc	tat	acc	cac	cag	2928	
Lys	Trp	Met	Ala	Leu	Glu	Ser	Ile	Leu	His	Arg	Ile	Tyr	Thr	His	Gln		
	880					885					890						
agt	gat	gtc	tgg	agc	tac	ggg	gtg	acc	gtt	tgg	gag	ttg	atg	acc	ttt	2976	
Ser	Asp	Val	Trp	Ser	Tyr	Gly	Val	Thr	Val	Trp	Glu	Leu	Met	Thr	Phe		
	895				900					905					910		
gga	tcc	aag	cca	tat	gac	gga	atc	cct	gcc	agc	gag	atc	tcc	tcc	atc	3024	
Gly	Ser	Lys	Pro	Tyr	Asp	Gly	Ile	Pro	Ala	Ser	Glu	Ile	Ser	Ser	Ile		
				915					920					925			
ctg	gag	aaa	gga	gaa	cgc	ctc	cct	cag	cca	ccc	ata	tgt	acc	atc	gat	3072	
Leu	Glu	Lys	Gly	Glu	Arg	Leu	Pro	Gln	Pro	Pro	Ile	Cys	Thr	Ile	Asp		
			930					935					940				
gtc	tac	atg	atc	atg	gtc	aag	tgc	tgg	atg	ata	gac	gca	gat	agt	cgc	3120	
Val	Tyr	Met	Ile	Met	Val	Lys	Cys	Trp	Met	Ile	Asp	Ala	Asp	Ser	Arg		
		945					950					955					
cca	aag	ttc	cgt	gag	ttg	atc	atc	gaa	ttc	tcc	aaa	atg	gcc	cga	gac	3168	
Pro	Lys	Phe	Arg	Glu	Leu	Ile	Ile	Glu	Phe	Ser	Lys	Met	Ala	Arg	Asp		
	960					965					970						
ccc	cag	cgc	tac	ctt	gtc	att	cag	ggg	gat	gaa	aga	atg	cat	ttg	cca	3216	
Pro	Gln	Arg	Tyr	Leu	Val	Ile	Gln	Gly	Asp	Glu	Arg	Met	His	Leu	Pro		
	975				980					985				990			
agt	cct	aca	gac	tcc	aac	ttc	tac	cgt	gcc	ctg	atg	gat	gaa	gaa	gac	3264	
Ser	Pro	Thr	Asp	Ser	Asn	Phe	Tyr	Arg	Ala	Leu	Met	Asp	Glu	Glu	Asp		
				995					1000					1005			
atg	gac	gac	gtg	gtg	gat	gcc	gac	gag	tac	ctc	atc	cca	cag	cag		3309	
Met	Asp	Asp	Val	Val	Asp	Ala	Asp	Glu	Tyr	Leu	Ile	Pro	Gln	Gln			
			1010					1015					1020				
ggc	ttc	ttc	agc	agc	ccc	tcc	acg	tca	cgg	act	ccc	ctc	ctg	agc		3354	
Gly	Phe	Phe	Ser	Ser	Pro	Ser	Thr	Ser	Arg	Thr	Pro	Leu	Leu	Ser			
			1025					1030					1035				
tct	ctg	agt	gca	acc	agc	aac	aat	tcc	acc	gtg	gct	tgc	att	gat		3399	
Ser	Leu	Ser	Ala	Thr	Ser	Asn	Asn	Ser	Thr	Val	Ala	Cys	Ile	Asp			
			1040					1045					1050				
aga	aat	ggg	ctg	caa	agc	tgt	ccc	atc	aag	gaa	gac	agc	ttc	ttg		3444	
Arg	Asn	Gly	Leu	Gln	Ser	Cys	Pro	Ile	Lys	Glu	Asp	Ser	Phe	Leu			
			1055					1060					1065				
cag	cga	tac	agc	tca	gac	ccc	aca	ggc	gcc	ttg	act	gag	gac	agc		3489	
Gln	Arg	Tyr	Ser	Ser	Asp	Pro	Thr	Gly	Ala	Leu	Thr	Glu	Asp	Ser			
			1070					1075					1080				
ata	gac	gac	acc	ttc	ctc	cca	gtg	cct	gaa	tac	ata	aac	cag	tcc		3534	
Ile	Asp	Asp	Thr	Phe	Leu	Pro	Val	Pro	Glu	Tyr	Ile	Asn	Gln	Ser			
			1085					1090					1095				

## 49321-137.ST25.txt

gtt ccc aaa agg ccc gct ggc tct	gtg cag aat cct gtc tat cac	3579
Val Pro Lys Arg Pro Ala Gly Ser	Val Gln Asn Pro Val Tyr His	
1100	1105 1110	
aat cag cct ctg aac ccc gcg ccc	agc aga gac cca cac tac cag	3624
Asn Gln Pro Leu Asn Pro Ala Pro	Ser Arg Asp Pro His Tyr Gln	
1115	1120 1125	
gac ccc cac agc act gca gtg ggc	aac ccc gag tat ctc aac act	3669
Asp Pro His Ser Thr Ala Val Gly	Asn Pro Glu Tyr Leu Asn Thr	
1130	1135 1140	
gtc cag ccc acc tgt gtc aac agc	aca ttc gac agc cct gcc cac	3714
Val Gln Pro Thr Cys Val Asn Ser	Thr Phe Asp Ser Pro Ala His	
1145	1150 1155	
tgg gcc cag aaa ggc agc cac caa	att agc ctg gac aac cct gac	3759
Trp Ala Gln Lys Gly Ser His Gln	Ile Ser Leu Asp Asn Pro Asp	
1160	1165 1170	
tac cag cag gac ttc ttt ccc aag	gaa gcc aag cca aat ggc atc	3804
Tyr Gln Gln Asp Phe Phe Pro Lys	Glu Ala Lys Pro Asn Gly Ile	
1175	1180 1185	
ttt aag ggc tcc aca gct gaa aat	gca gaa tac cta agg gtc gcg	3849
Phe Lys Gly Ser Thr Ala Glu Asn	Ala Glu Tyr Leu Arg Val Ala	
1190	1195 1200	
cca caa agc agt gaa ttt att gga	gca tga ccacggagga tagtatgagc	3899
Pro Gln Ser Ser Glu Phe Ile Gly	Ala	
1205	1210	
cctaaaaatc cagactcttt cgatacccag	gaccaagcca cagcaggtcc tccatcccaa	3959
cagccatgcc cgcattagct cttagaccca	cagactgggt ttgcaacgtt tacaccgact	4019
agccaggaag tacttccacc tcgggcacat	tttgggaagt tgcattcctt tgtcttcaaa	4079
ctgtgaagca tttacagaaa cgcatccagc	aagaatattg tccctttgag cagaaattta	4139
tctttcaaag aggtatatatt gaaaaaaaa	aaaagtatat gtgaggattt ttattgattg	4199
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ggaagaagct tgctggtagc acttgctacc	ctgagttcat ccaggcccaa ctgtgagcaa	4319
ggagcacaag ccacaagtct tccagaggat	gcttgattcc agtgggtctg cttcaaggct	4379
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actgtatcaa gtcattggcag gtacagtagg	ataagccact ctgtcccttc ctgggcaaag	4499
aagaaacgga ggggatggaa ttcttcctta	gacttacttt tgtaaaaatg tccccacggt	4559
acttactccc cactgatgga ccagtgggtt	ccagtcatga gcgttagact gacttgtttg	4619
tcttccattc cattgttttg aaactcagta	tgctgccct gtcttgctgt catgaaatca	4679
gcaagagagg atgacacatc aaataataac	tcggattcca gccacattg gattcatcag	4739

## 49321-137.ST25.txt

catttgacc aatagccac agctgagaat gtggaatacc taaggatagc accgcttttg 4799  
ttctcgcaaa aacgtatctc ctaatttgag gctcagatga aatgcatcag gtcctttggg 4859  
gcatagatca gaagactaca aaaatgaagc tgctctgaaa tctccttttag ccatcacccc 4919  
aaccccccaa aattagtttg tgttacttat ggaagatagt tttctccttt tacttcactt 4979  
caaaagcttt ttactcaaag agtatatgtt ccctccaggt cagctgcccc caaacccctt 5039  
ccttacgctt tgtcacacaa aaagtgtctc tgccttgagt catctattca agcacttaca 5099  
gctctggcca caacagggca ttttacaggt gcgaatgaca gtagcattat gagtagtgtg 5159  
gaattcaggt agtaaatatg aaactagggt ttgaaattga taatgctttc acaacatttg 5219  
cagatgtttt agaaggaaaa agttccttc ctaaaataat ttctctacaa ttggaagatt 5279  
ggaagattca gctagttagg agcccacctt ttttcctaatt ctgtgtgtgc cctgtaacct 5339  
gactgggtaa cagcagtcct ttgtaaacag tgttttaaag tctcctagtc aatatccacc 5399  
ccatccaatt tatcaaggaa gaaatggttc agaaaatatt ttcagcctac agttatgttc 5459  
agtcacacac acatacaaaa tgttcctttt gcttttaaag taatttttga ctcccagatc 5519  
agtcagagcc cctacagcat tgtaagaaa gtatttgatt tttgtctcaa tgaaaataaa 5579  
actatattca tttccactct aaaaaaaaaa aaaaaaa 5616

<210> 6  
<211> 1210  
<212> PRT  
<213> Homo sapiens

<400> 6

Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala  
1 5 10 15

Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln  
20 25 30

Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe  
35 40 45

Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn  
50 55 60

Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys  
65 70 75 80

## 49321-137.ST25.txt

Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val  
 85 90 95

Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr  
 100 105 110

Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn  
 115 120 125

Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu  
 130 135 140

His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu  
 145 150 155 160

Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met  
 165 170 175

Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro  
 180 185 190

Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln  
 195 200 205

Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg  
 210 215 220

Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys  
 225 230 235 240

Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp  
 245 250 255

Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro  
 260 265 270

Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly  
 275 280 285

Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His  
 290 295 300

Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu  
 305 310 315 320

49321-137.ST25.txt

Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val  
 325 330 335

Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn  
 340 345 350

Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp  
 355 360 365

Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr  
 370 375 380

Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys Glu  
 385 390 395 400

Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp  
 405 410 415

Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln  
 420 425 430

His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu  
 435 440 445

Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser  
 450 455 460

Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu  
 465 470 475 480

Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu  
 485 490 495

Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro  
 500 505 510

Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn  
 515 520 525

Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly  
 530 535 540

Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro  
 545 550 555 560

49321-137.ST25.txt

Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro  
 565 570 575

Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val  
 580 585 590

Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp  
 595 600 605

Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys  
 610 615 620

Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly  
 625 630 635 640

Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu  
 645 650 655

Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His  
 660 665 670

Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu  
 675 680 685

Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu  
 690 695 700

Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser  
 705 710 715 720

Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu  
 725 730 735

Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser  
 740 745 750

Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser  
 755 760 765

Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser  
 770 775 780

Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp

49321-137.ST25.txt

785	790	795	800
Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn	805	810	815
Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg	820	825	830
Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro	835	840	845
Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala	850	855	860
Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp	865	870	875
Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp	885	890	895
Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser	900	905	910
Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu	915	920	925
Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr	930	935	940
Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys	945	950	955
Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln	965	970	975
Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro	980	985	990
Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp	995	1000	1005
Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe	1010	1015	1020

## 49321-137.ST25.txt

Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu  
 1025 1030 1035

Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn  
 1040 1045 1050

Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg  
 1055 1060 1065

Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp  
 1070 1075 1080

Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro  
 1085 1090 1095

Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln  
 1100 1105 1110

Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro  
 1115 1120 1125

His Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln  
 1130 1135 1140

Pro Thr Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala  
 1145 1150 1155

Gln Lys Gly Ser His Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln  
 1160 1165 1170

Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn Gly Ile Phe Lys  
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Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val Ala Pro Gln  
 1190 1195 1200

Ser Ser Glu Phe Ile Gly Ala  
 1205 1210

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<220>



49321-137.ST25.txt

&lt;221&gt; CDS

&lt;222&gt; (247)..(3078)

&lt;223&gt; delta EGFR coding sequence [represents in-frame deletion of 801 bp (275-1027) of the ECD of EGFR corresponding to exons 2-7 of the gene]

&lt;400&gt; 7

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aggccacctc gtcggcggtcc gcccgagtcc ccgcctcgcc gccaacgcca caaccaccgc      180
gcacggcccc ctgactccgt ccagtattga tcgggagagc cggagcgagc tcttcgggga      240
gcagcg atg cga ccc tcc ggg acg gcc ggg gca gtg gat gtg aac ccc      288
      Met Arg Pro Ser Gly Thr Ala Gly Ala Val Asp Val Asn Pro
      1          5          10

gag ggc aaa tac agc ttt ggt gcc acc tgc gtg aag aag tgt ccc cgt      336
Glu Gly Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro Arg
15          20          25          30

aat tat gtg gtg aca gat cac ggc tcg tgc gtc cga gcc tgt ggg gcc      384
Asn Tyr Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala
          35          40          45

gac agc tat gag atg gag gaa gac ggc gtc cgc aag tgt aag aag tgc      432
Asp Ser Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys
          50          55          60

gaa ggg cct tgc cgc aaa gtg tgt aac gga ata ggt att ggt gaa ttt      480
Glu Gly Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe
65          70          75

aaa gac tca ctc tcc ata aat gct acg aat att aaa cac ttc aaa aac      528
Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn
80          85          90

tgc acc tcc atc agt ggc gat ctc cac atc ctg ccg gtg gca ttt agg      576
Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg
95          100          105          110

ggt gac tcc ttc aca cat act cct cct ctg gat cca cag gaa ctg gat      624
Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp
          115          120          125

att ctg aaa acc gta aag gaa atc aca ggg ttt ttg ctg att cag gct      672
Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala
          130          135          140

tgg cct gaa aac agg acg gac ctc cat gcc ttt gag aac cta gaa atc      720
Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile
          145          150          155

ata cgc ggc agg acc aag caa cat ggt cag ttt tct ctt gca gtc gtc      768
Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val
          160          165          170

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## 49321-137.ST25.txt

agc ctg aac ata aca tcc ttg gga tta cgc tcc ctc aag gag ata agt	816
Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser	
175 180 185 190	
gat gga gat gtg ata att tca gga aac aaa aat ttg tgc tat gca aat	864
Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn	
195 200 205	
aca ata aac tgg aaa aaa ctg ttt ggg acc tcc ggt cag aaa acc aaa	912
Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys	
210 215 220	
att ata agc aac aga ggt gaa aac agc tgc aag gcc aca ggc cag gtc	960
Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val	
225 230 235	
tgc cat gcc ttg tgc tcc ccc gag ggc tgc tgg ggc ccg gag ccc agg	1008
Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg	
240 245 250	
gac tgc gtc tct tgc cgg aat gtc agc cga ggc agg gaa tgc gtg gac	1056
Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp	
255 260 265 270	
aag tgc aac ctt ctg gag ggt gag cca agg gag ttt gtg gag aac tct	1104
Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser	
275 280 285	
gag tgc ata cag tgc cac cca gag tgc ctg cct cag gcc atg aac atc	1152
Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile	
290 295 300	
acc tgc aca gga cgg gga cca gac aac tgt atc cag tgt gcc cac tac	1200
Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr	
305 310 315	
att gac ggc ccc cac tgc gtc aag acc tgc ccg gca gga gtc atg gga	1248
Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly	
320 325 330	
gaa aac aac acc ctg gtc tgg aag tac gca gac gcc ggc cat gtg tgc	1296
Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys	
335 340 345 350	
cac ctg tgc cat cca aac tgc acc tac gga tgc act ggg cca ggt ctt	1344
His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu	
355 360 365	
gaa ggc tgt cca acg aat ggg cct aag atc ccg tcc atc gcc act ggg	1392
Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly	
370 375 380	
atg gtg ggg gcc ctc ctc ttg ctg ctg gtg gtg gcc ctg ggg atc ggc	1440
Met Val Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly	
385 390 395	
ctc ttc atg cga agg cgc cac atc gtt cgg aag cgc acg ctg cgg agg	1488
Leu Phe Met Arg Arg Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg	
400 405 410	

## 49321-137.ST25.txt

ctg ctg cag gag agg gag ctt gtg gag cct ctt aca ccc agt gga gaa	1536
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gct ccc aac caa gct ctc ttg agg atc ttg aag gaa act gaa ttc aaa	1584
Ala Pro Asn Gln Ala Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys	
435 440 445	
aag atc aaa gtg ctg ggc tcc ggt gcg ttc ggc acg gtg tat aag gga	1632
Lys Ile Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly	
450 455 460	
ctc tgg atc cca gaa ggt gag aaa gtt aaa att ccc gtc gct atc aag	1680
Leu Trp Ile Pro Glu Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys	
465 470 475	
gaa tta aga gaa gca aca tct ccg aaa gcc aac aag gaa atc ctc gat	1728
Glu Leu Arg Glu Ala Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp	
480 485 490	
gaa gcc tac gtg atg gcc agc gtg gac aac ccc cac gtg tgc cgc ctg	1776
Glu Ala Tyr Val Met Ala Ser Val Asp Asn Pro His Val Cys Arg Leu	
495 500 505 510	
ctg ggc atc tgc ctc acc tcc acc gtg cag ctc atc acg cag ctc atg	1824
Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met	
515 520 525	
ccc ttc ggc tgc ctc ctg gac tat gtc cgg gaa cac aaa gac aat att	1872
Pro Phe Gly Cys Leu Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile	
530 535 540	
ggc tcc cag tac ctg ctc aac tgg tgt gtg cag atc gca aag ggc atg	1920
Gly Ser Gln Tyr Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met	
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aac tac ttg gag gac cgt cgc ttg gtg cac cgc gac ctg gca gcc agg	1968
Asn Tyr Leu Glu Asp Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg	
560 565 570	
aac gta ctg gtg aaa aca ccg cag cat gtc aag atc aca gat ttt ggg	2016
Asn Val Leu Val Lys Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly	
575 580 585 590	
ctg gcc aaa ctg ctg ggt gcg gaa gag aaa gaa tac cat gca gaa gga	2064
Leu Ala Lys Leu Leu Gly Ala Glu Glu Lys Glu Tyr His Ala Glu Gly	
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ggc aaa gtg cct atc aag tgg atg gca ttg gaa tca att tta cac aga	2112
Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg	
610 615 620	
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Ile Tyr Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp	
625 630 635	
gag ttg atg acc ttt gga tcc aag cca tat gac gga atc cct gcc agc	2208
Glu Leu Met Thr Phe Gly Ser Lys Pro Tyr Asp Gly Ile Pro Ala Ser	

49321-137.ST25.txt

640	645	650	
gag atc tcc tcc atc ctg gag aaa gga gaa cgc ctc cct cag cca ccc Glu Ile Ser Ser Ile Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro 655 660 665 670			2256
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gac gca gat agt cgc cca aag ttc cgt gag ttg atc atc gaa ttc tcc Asp Ala Asp Ser Arg Pro Lys Phe Arg Glu Leu Ile Ile Glu Phe Ser 690 695 700			2352
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aga atg cat ttg cca agt cct aca gac tcc aac ttc tac cgt gcc ctg Arg Met His Leu Pro Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala Leu 720 725 730			2448
atg gat gaa gaa gac atg gac gac gtg gtg gat gcc gac gag tac ctc Met Asp Glu Glu Asp Met Asp Asp Val Val Asp Ala Asp Glu Tyr Leu 735 740 745 750			2496
atc cca cag cag ggc ttc ttc agc agc ccc tcc acg tca cgg act ccc Ile Pro Gln Gln Gly Phe Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro 755 760 765			2544
ctc ctg agc tct ctg agt gca acc agc aac aat tcc acc gtg gct tgc Leu Leu Ser Ser Leu Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys 770 775 780			2592
att gat aga aat ggg ctg caa agc tgt ccc atc aag gaa gac agc ttc Ile Asp Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe 785 790 795			2640
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ata gac gac acc ttc ctc cca gtg cct gaa tac ata aac cag tcc gtt Ile Asp Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val 815 820 825 830			2736
ccc aaa agg ccc gct ggc tct gtg cag aat cct gtc tat cac aat cag Pro Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln 835 840 845			2784
cct ctg aac ccc gcg ccc agc aga gac cca cac tac cag gac ccc cac Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro His 850 855 860			2832
agc act gca gtg ggc aac ccc gag tat ctc aac act gtc cag ccc acc Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln Pro Thr 865 870 875			2880
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## 49321-137.ST25.txt

Cys	Val	Asn	Ser	Thr	Phe	Asp	Ser	Pro	Ala	His	Trp	Ala	Gln	Lys	Gly	
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Ser	His	Gln	Ile	Ser	Leu	Asp	Asn	Pro	Asp	Tyr	Gln	Gln	Asp	Phe	Phe	
895					900				905						910	
ccc	aag	gaa	gcc	aag	cca	aat	ggc	atc	ttt	aag	ggc	tcc	aca	gct	gaa	3024
Pro	Lys	Glu	Ala	Lys	Pro	Asn	Gly	Ile	Phe	Lys	Gly	Ser	Thr	Ala	Glu	
				915					920					925		
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Asn	Ala	Glu	Tyr	Leu	Arg	Val	Ala	Pro	Gln	Ser	Ser	Glu	Phe	Ile	Gly	
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Ala																
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## 49321-137.ST25.txt

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 agaaaatatt ttcagcctac agttatgttc agtcacacac acatacaaaa tgttcctttt 4688  
 gcttttaaaag taatttttga ctcccagatc agtcagagcc cctacagcat tgtaagaaa 4748  
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 35 40 45

Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly  
 50 55 60

Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp  
 65 70 75 80

Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr  
 85 90 95

Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp  
 100 105 110

Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu  
 115 120 125

Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro

49321-137.ST25.txt

130

135

140

Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg  
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Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu  
 165 170 175

Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly  
 180 185 190

Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile  
 195 200 205

Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile  
 210 215 220

Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His  
 225 230 235 240

Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys  
 245 250 255

Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys  
 260 265 270

Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys  
 275 280 285

Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys  
 290 295 300

Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp  
 305 310 315 320

Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn  
 325 330 335

Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu  
 340 345 350

Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly  
 355 360 365

49321-137.ST25.txt

Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val  
 370 375 380

Gly Ala Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe  
 385 390 395 400

Met Arg Arg Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu  
 405 410 415

Gln Glu Arg Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro  
 420 425 430

Asn Gln Ala Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile  
 435 440 445

Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp  
 450 455 460

Ile Pro Glu Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu  
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Arg Glu Ala Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala  
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Tyr Val Met Ala Ser Val Asp Asn Pro His Val Cys Arg Leu Leu Gly  
 500 505 510

Ile Cys Leu Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe  
 515 520 525

Gly Cys Leu Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser  
 530 535 540

Gln Tyr Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr  
 545 550 555 560

Leu Glu Asp Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn Val  
 565 570 575

Leu Val Lys Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala  
 580 585 590

Lys Leu Leu Gly Ala Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys  
 595 600 605



## 49321-137.ST25.txt

Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr  
610 615 620

Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu  
625 630 635 640

Met Thr Phe Gly Ser Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile  
645 650 655

Ser Ser Ile Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys  
660 665 670

Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met Ile Asp Ala  
675 680 685

Asp Ser Arg Pro Lys Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met  
690 695 700

Ala Arg Asp Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met  
705 710 715 720

His Leu Pro Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp  
725 730 735

Glu Glu Asp Met Asp Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro  
740 745 750

Gln Gln Gly Phe Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu  
755 760 765

Ser Ser Leu Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp  
770 775 780

Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln  
785 790 795 800

Arg Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp  
805 810 815

Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys  
820 825 830

Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu  
835 840 845

## 49321-137.ST25.txt

Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr  
850 855 860

Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val  
865 870 875 880

Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala Gln Lys Gly Ser His  
885 890 895

Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys  
900 905 910

Glu Ala Lys Pro Asn Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala  
915 920 925

Glu Tyr Leu Arg Val Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala  
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agccatgggg ccggagccgc agtgagcacc atg gag ctg gcg gcc ttg tgc cgc 174  
Met Glu Leu Ala Ala Leu Cys Arg  
1 5  
tgg ggg ctc ctc ctc gcc ctc ttg ccc ccc gga gcc gcg agc acc caa 222  
Trp Gly Leu Leu Leu Ala Leu Leu Pro Pro Gly Ala Ala Ser Thr Gln  
10 15 20  
gtg tgc acc ggc aca gac atg aag ctg cgg ctc cct gcc agt ccc gag 270  
Val Cys Thr Gly Thr Asp Met Lys Leu Arg Leu Pro Ala Ser Pro Glu  
25 30 35 40  
acc cac ctg gac atg ctc cgc cac ctc tac cag ggc tgc cag gtg gtg 318  
Thr His Leu Asp Met Leu Arg His Leu Tyr Gln Gly Cys Gln Val Val  
45 50 55  
cag gga aac ctg gaa ctc acc tac ctg ccc acc aat gcc agc ctg tcc 366

## 49321-137.ST25.txt

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Phe	Leu	Gln	Asp	Ile	Gln	Glu	Val	Gln	Gly	Tyr	Val	Leu	Ile	Ala	His	
75				80				85								
aac	caa	gtg	agg	cag	gtc	cca	ctg	cag	agg	ctg	cgg	att	gtg	cga	ggc	462
Asn	Gln	Val	Arg	Gln	Val	Pro	Leu	Gln	Arg	Leu	Arg	Ile	Val	Arg	Gly	
90				95				100								
acc	cag	ctc	ttt	gag	gac	aac	tat	gcc	ctg	gcc	gtg	cta	gac	aat	gga	510
Thr	Gln	Leu	Phe	Glu	Asp	Asn	Tyr	Ala	Leu	Ala	Val	Leu	Asp	Asn	Gly	
105				110				115				120				
gac	ccg	ctg	aac	aat	acc	acc	cct	gtc	aca	ggg	gcc	tcc	cca	gga	ggc	558
Asp	Pro	Leu	Asn	Asn	Thr	Thr	Pro	Val	Thr	Gly	Ala	Ser	Pro	Gly	Gly	
125				130				135								
ctg	cgg	gag	ctg	cag	ctt	cga	agc	ctc	aca	gag	atc	ttg	aaa	gga	ggg	606
Leu	Arg	Glu	Leu	Gln	Leu	Arg	Ser	Leu	Thr	Glu	Ile	Leu	Lys	Gly	Gly	
140				145				150								
gtc	ttg	atc	cag	cgg	aac	ccc	cag	ctc	tgc	tac	cag	gac	acg	att	ttg	654
Val	Leu	Ile	Gln	Arg	Asn	Pro	Gln	Leu	Cys	Tyr	Gln	Asp	Thr	Ile	Leu	
155				160				165								
tgg	aag	gac	atc	ttc	cac	aag	aac	aac	cag	ctg	gct	ctc	aca	ctg	ata	702
Trp	Lys	Asp	Ile	Phe	His	Lys	Asn	Asn	Gln	Leu	Ala	Leu	Thr	Leu	Ile	
170				175				180								
gac	acc	aac	cgc	tct	cgg	gcc	tgc	cac	ccc	tgt	tct	ccg	atg	tgt	aag	750
Asp	Thr	Asn	Arg	Ser	Arg	Ala	Cys	His	Pro	Cys	Ser	Pro	Met	Cys	Lys	
185				190				195				200				
ggc	tcc	cgc	tgc	tgg	gga	gag	agt	tct	gag	gat	tgt	cag	agc	ctg	acg	798
Gly	Ser	Arg	Cys	Trp	Gly	Glu	Ser	Ser	Glu	Asp	Cys	Gln	Ser	Leu	Thr	
205				210				215								
cgc	act	gtc	tgt	gcc	ggg	ggc	tgt	gcc	cgc	tgc	aag	ggg	cca	ctg	ccc	846
Arg	Thr	Val	Cys	Ala	Gly	Gly	Cys	Ala	Arg	Cys	Lys	Gly	Pro	Leu	Pro	
220				225				230								
act	gac	tgc	tgc	cat	gag	cag	tgt	gct	gcc	ggc	tgc	acg	ggc	ccc	aag	894
Thr	Asp	Cys	Cys	His	Glu	Gln	Cys	Ala	Ala	Gly	Cys	Thr	Gly	Pro	Lys	
235				240				245								
cac	tct	gac	tgc	ctg	gcc	tgc	ctc	cac	ttc	aac	cac	agt	ggc	atc	tgt	942
His	Ser	Asp	Cys	Leu	Ala	Cys	Leu	His	Phe	Asn	His	Ser	Gly	Ile	Cys	
250				255				260								
gag	ctg	cac	tgc	cca	gcc	ctg	gtc	acc	tac	aac	aca	gac	acg	ttt	gag	990
Glu	Leu	His	Cys	Pro	Ala	Leu	Val	Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	
265				270				275				280				
tcc	atg	ccc	aat	ccc	gag	ggc	cgg	tat	aca	ttc	ggc	gcc	agc	tgt	gtg	1038
Ser	Met	Pro	Asn	Pro	Glu	Gly	Arg	Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	
285				290				295								

## 49321-137.ST25.txt

act gcc tgt ccc tac aac tac ctt tct acg gac gtg gga tcc tgc acc	1086
Thr Ala Cys Pro Tyr Asn Tyr Leu Ser Thr Asp Val Gly Ser Cys Thr	
300 305 310	
ctc gtc tgc ccc ctg cac aac caa gag gtg aca gca gag gat gga aca	1134
Leu Val Cys Pro Leu His Asn Gln Glu Val Thr Ala Glu Asp Gly Thr	
315 320 325	
cag cgg tgt gag aag tgc agc aag ccc tgt gcc cga gtg tgc tat ggt	1182
Gln Arg Cys Glu Lys Cys Ser Lys Pro Cys Ala Arg Val Cys Tyr Gly	
330 335 340	
ctg ggc atg gag cac ttg cga gag gtg agg gca gtt acc agt gcc aat	1230
Leu Gly Met Glu His Leu Arg Glu Val Arg Ala Val Thr Ser Ala Asn	
345 350 355 360	
atc cag gag ttt gct ggc tgc aag aag atc ttt ggg agc ctg gca ttt	1278
Ile Gln Glu Phe Ala Gly Cys Lys Lys Ile Phe Gly Ser Leu Ala Phe	
365 370 375	
ctg ccg gag agc ttt gat ggg gac cca gcc tcc aac act gcc ccg ctc	1326
Leu Pro Glu Ser Phe Asp Gly Asp Pro Ala Ser Asn Thr Ala Pro Leu	
380 385 390	
cag cca gag cag ctc caa gtg ttt gag act ctg gaa gag atc aca ggt	1374
Gln Pro Glu Gln Leu Gln Val Phe Glu Thr Leu Glu Glu Ile Thr Gly	
395 400 405	
tac cta tac atc tca gca tgg ccg gac agc ctg cct gac ctc agc gtc	1422
Tyr Leu Tyr Ile Ser Ala Trp Pro Asp Ser Leu Pro Asp Leu Ser Val	
410 415 420	
ttc cag aac ctg caa gta atc cgg gga cga att ctg cac aat ggc gcc	1470
Phe Gln Asn Leu Gln Val Ile Arg Gly Arg Ile Leu His Asn Gly Ala	
425 430 435 440	
tac tcg ctg acc ctg caa ggg ctg ggc atc agc tgg ctg ggg ctg cgc	1518
Tyr Ser Leu Thr Leu Gln Gly Leu Gly Ile Ser Trp Leu Gly Leu Arg	
445 450 455	
tca ctg agg gaa ctg ggc agt gga ctg gcc ctc atc cac cat aac acc	1566
Ser Leu Arg Glu Leu Gly Ser Gly Leu Ala Leu Ile His His Asn Thr	
460 465 470	
cac ctc tgc ttc gtg cac acg gtg ccc tgg gac cag ctc ttt cgg aac	1614
His Leu Cys Phe Val His Thr Val Pro Trp Asp Gln Leu Phe Arg Asn	
475 480 485	
ccg cac caa gct ctg ctc cac act gcc aac cgg cca gag gac gag tgt	1662
Pro His Gln Ala Leu Leu His Thr Ala Asn Arg Pro Glu Asp Glu Cys	
490 495 500	
gtg ggc gag ggc ctg gcc tgc cac cag ctg tgc gcc cga ggg cac tgc	1710
Val Gly Glu Gly Leu Ala Cys His Gln Leu Cys Ala Arg Gly His Cys	
505 510 515 520	
tgg ggt cca ggg ccc acc cag tgt gtc aac tgc agc cag ttc ctt cgg	1758
Trp Gly Pro Gly Pro Thr Gln Cys Val Asn Cys Ser Gln Phe Leu Arg	
525 530 535	

## 49321-137.ST25.txt

ggc cag gag tgc gtg gag gaa tgc cga gta ctg cag ggg ctc ccc agg	1806
Gly Gln Glu Cys Val Glu Glu Cys Arg Val Leu Gln Gly Leu Pro Arg	
540 545 550	
gag tat gtg aat gcc agg cac tgt ttg ccg tgc cac cct gag tgt cag	1854
Glu Tyr Val Asn Ala Arg His Cys Leu Pro Cys His Pro Glu Cys Gln	
555 560 565	
ccc cag aat ggc tca gtg acc tgt ttt gga ccg gag gct gac cag tgt	1902
Pro Gln Asn Gly Ser Val Thr Cys Phe Gly Pro Glu Ala Asp Gln Cys	
570 575 580	
gtg gcc tgt gcc cac tat aag gac cct ccc ttc tgc gtg gcc cgc tgc	1950
Val Ala Cys Ala His Tyr Lys Asp Pro Pro Phe Cys Val Ala Arg Cys	
585 590 595 600	
ccc agc ggt gtg aaa cct gac ctc tcc tac atg ccc atc tgg aag ttt	1998
Pro Ser Gly Val Lys Pro Asp Leu Ser Tyr Met Pro Ile Trp Lys Phe	
605 610 615	
cca gat gag gag ggc gca tgc cag cct tgc ccc atc aac tgc acc cac	2046
Pro Asp Glu Glu Gly Ala Cys Gln Pro Cys Pro Ile Asn Cys Thr His	
620 625 630	
tcc tgt gtg gac ctg gat gac aag ggc tgc ccc gcc gag cag aga gcc	2094
Ser Cys Val Asp Leu Asp Asp Lys Gly Cys Pro Ala Glu Gln Arg Ala	
635 640 645	
agc cct ctg acg tcc atc gtc tct gcg gtg gtt ggc att ctg ctg gtc	2142
Ser Pro Leu Thr Ser Ile Val Ser Ala Val Val Gly Ile Leu Leu Val	
650 655 660	
gtg gtc ttg ggg gtg gtc ttt ggg atc ctc atc aag cga cgg cag cag	2190
Val Val Leu Gly Val Val Phe Gly Ile Leu Ile Lys Arg Arg Gln Gln	
665 670 675 680	
aag atc cgg aag tac acg atg cgg aga ctg ctg cag gaa acg gag ctg	2238
Lys Ile Arg Lys Tyr Thr Met Arg Arg Leu Leu Gln Glu Thr Glu Leu	
685 690 695	
gtg gag ccg ctg aca cct agc gga gcg atg ccc aac cag gcg cag atg	2286
Val Glu Pro Leu Thr Pro Ser Gly Ala Met Pro Asn Gln Ala Gln Met	
700 705 710	
cgg atc ctg aaa gag acg gag ctg agg aag gtg aag gtg ctt gga tct	2334
Arg Ile Leu Lys Glu Thr Glu Leu Arg Lys Val Lys Val Leu Gly Ser	
715 720 725	
ggc gct ttt ggc aca gtc tac aag ggc atc tgg atc cct gat ggg gag	2382
Gly Ala Phe Gly Thr Val Tyr Lys Gly Ile Trp Ile Pro Asp Gly Glu	
730 735 740	
aat gtg aaa att cca gtg gcc atc aaa gtg ttg agg gaa aac aca tcc	2430
Asn Val Lys Ile Pro Val Ala Ile Lys Val Leu Arg Glu Asn Thr Ser	
745 750 755 760	
ccc aaa gcc aac aaa gaa atc tta gac gaa gca tac gtg atg gct ggt	2478
Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Gly	

## 49321-137.ST25.txt

765										770										775										
gtg ggc tcc cca tat gtc tcc cgc ctt ctg ggc atc tgc ctg aca tcc	2526																													
Val Gly Ser Pro Tyr Val Ser Arg Leu Leu Gly Ile Cys Leu Thr Ser																														
780	785	790																												
acg gtg cag ctg gtg aca cag ctt atg ccc tat ggc tgc ctc tta gac	2574																													
Thr Val Gln Leu Val Thr Gln Leu Met Pro Tyr Gly Cys Leu Leu Asp																														
795	800	805																												
cat gtc cgg gaa aac cgc gga cgc ctg ggc tcc cag gac ctg ctg aac	2622																													
His Val Arg Glu Asn Arg Gly Arg Leu Gly Ser Gln Asp Leu Leu Asn																														
810	815	820																												
tgg tgt atg cag att gcc aag ggg atg agc tac ctg gag gat gtg cgg	2670																													
Trp Cys Met Gln Ile Ala Lys Gly Met Ser Tyr Leu Glu Asp Val Arg																														
825	830	835	840																											
ctc gta cac agg gac ttg gcc gct cgg aac gtg ctg gtc aag agt ccc	2718																													
Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Ser Pro																														
845	850	855																												
aac cat gtc aaa att aca gac ttc ggg ctg gct cgg ctg ctg gac att	2766																													
Asn His Val Lys Ile Thr Asp Phe Gly Leu Ala Arg Leu Leu Asp Ile																														
860	865	870																												
gac gag aca gag tac cat gca gat ggg ggc aag gtg ccc atc aag tgg	2814																													
Asp Glu Thr Glu Tyr His Ala Asp Gly Gly Lys Val Pro Ile Lys Trp																														
875	880	885																												
atg gcg ctg gag tcc att ctc cgc cgg cgg ttc acc cac cag agt gat	2862																													
Met Ala Leu Glu Ser Ile Leu Arg Arg Arg Phe Thr His Gln Ser Asp																														
890	895	900																												
gtg tgg agt tat ggt gtg act gtg tgg gag ctg atg act ttt ggg gcc	2910																													
Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala																														
905	910	915	920																											
aaa cct tac gat ggg atc cca gcc cgg gag atc cct gac ctg ctg gaa	2958																													
Lys Pro Tyr Asp Gly Ile Pro Ala Arg Glu Ile Pro Asp Leu Leu Glu																														
925	930	935																												
aag ggg gag cgg ctg ccc cag ccc ccc atc tgc acc att gat gtc tac	3006																													
Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr																														
940	945	950																												
atg atc atg gtc aaa tgt tgg atg att gac tct gaa tgt cgg cca aga	3054																													
Met Ile Met Val Lys Cys Trp Met Ile Asp Ser Glu Cys Arg Pro Arg																														
955	960	965																												
ttc cgg gag ttg gtg tct gaa ttc tcc cgc atg gcc agg gac ccc cag	3102																													
Phe Arg Glu Leu Val Ser Glu Phe Ser Arg Met Ala Arg Asp Pro Gln																														
970	975	980																												
cgc ttt gtg gtc atc cag aat gag gac ttg ggc cca gcc agt ccc ttg	3150																													
Arg Phe Val Val Ile Gln Asn Glu Asp Leu Gly Pro Ala Ser Pro Leu																														
985	990	995	1000																											
gac agc acc ttc tac cgc tca ctg ctg gag gac gat gac atg ggg	3195																													

## 49321-137.ST25.txt

Asp Ser Thr Phe Tyr	Arg Ser Leu Leu Glu	Asp Asp Asp Met Gly	
1005	1010	1015	
gac ctg gtg gat gct	gag gag tat ctg gta	ccc cag cag ggc ttc	3240
Asp Leu Val Asp Ala	Glu Glu Tyr Leu Val	Pro Gln Gln Gly Phe	
1020	1025	1030	
ttc tgt cca gac cct	gcc ccg ggc gct ggg	ggc atg gtc cac cac	3285
Phe Cys Pro Asp Pro	Ala Pro Gly Ala Gly	Gly Met Val His His	
1035	1040	1045	
agg cac cgc agc tca	tct acc agg agt ggc	ggg gac ctg aca	3330
Arg His Arg Ser Ser	Ser Thr Arg Ser Gly	Gly Gly Asp Leu Thr	
1050	1055	1060	
cta ggg ctg gag ccc	tct gaa gag gag gcc	ccc agg tct cca ctg	3375
Leu Gly Leu Glu Pro	Ser Glu Glu Glu Ala	Pro Arg Ser Pro Leu	
1065	1070	1075	
gca ccc tcc gaa ggg	gct ggc tcc gat gta	ttt gat ggt gac ctg	3420
Ala Pro Ser Glu Gly	Ala Gly Ser Asp Val	Phe Asp Gly Asp Leu	
1080	1085	1090	
gga atg ggg gca gcc	aag ggg ctg caa agc	ctc ccc aca cat gac	3465
Gly Met Gly Ala Ala	Lys Gly Leu Gln Ser	Leu Pro Thr His Asp	
1095	1100	1105	
ccc agc cct cta cag	cgg tac agt gag gac	ccc aca gta ccc ctg	3510
Pro Ser Pro Leu Gln	Arg Tyr Ser Glu Asp	Pro Thr Val Pro Leu	
1110	1115	1120	
ccc tct gag act gat	ggc tac gtt gcc ccc	ctg acc tgc agc ccc	3555
Pro Ser Glu Thr Asp	Gly Tyr Val Ala Pro	Leu Thr Cys Ser Pro	
1125	1130	1135	
cag cct gaa tat gtg	aac cag cca gat gtt	cgg ccc cag ccc cct	3600
Gln Pro Glu Tyr Val	Asn Gln Pro Asp Val	Arg Pro Gln Pro Pro	
1140	1145	1150	
tcg ccc cga gag ggc	cct ctg cct gct gcc	cga cct gct ggt gcc	3645
Ser Pro Arg Glu Gly	Pro Leu Pro Ala Ala	Arg Pro Ala Gly Ala	
1155	1160	1165	
act ctg gaa agg gcc	aag act ctc tcc cca	ggg aag aat ggg gtc	3690
Thr Leu Glu Arg Ala	Lys Thr Leu Ser Pro	Gly Lys Asn Gly Val	
1170	1175	1180	
gtc aaa gac gtt ttt	gcc ttt ggg ggt gcc	gtg gag aac ccc gag	3735
Val Lys Asp Val Phe	Ala Phe Gly Gly Ala	Val Glu Asn Pro Glu	
1185	1190	1195	
tac ttg aca ccc cag	gga gga gct gcc cct	cag ccc cac cct cct	3780
Tyr Leu Thr Pro Gln	Gly Gly Ala Ala Pro	Gln Pro His Pro Pro	
1200	1205	1210	
cct gcc ttc agc cca	gcc ttc gac aac ctc	tat tac tgg gac cag	3825
Pro Ala Phe Ser Pro	Ala Phe Asp Asn Leu	Tyr Tyr Trp Asp Gln	
1215	1220	1225	

## 49321-137.ST25.txt

gac cca cca gag cgg ggg gct cca ccc agc acc ttc aaa ggg aca 3870  
 Asp Pro Pro Glu Arg Gly Ala Pro Pro Ser Thr Phe Lys Gly Thr  
 1230 1235 1240

cct acg gca gag aac cca gag tac ctg ggt ctg gac gtg cca gtg 3915  
 Pro Thr Ala Glu Asn Pro Glu Tyr Leu Gly Leu Asp Val Pro Val  
 1245 1250 1255

tga accagaaggc caagtccgca gaagccctga tgtgtcctca gggagcaggg 3968

aaggcctgac ttctgctggc atcaagaggt gggagggccc tccgaccact tccaggggaa 4028

cctgccatgc caggaacctg tcctaaggaa ccttccttcc tgcttgagtt cccagatggc 4088

tggaaggggt ccagcctcgt tggaagagga acagcactgg ggagtctttg tggattctga 4148

ggccctgccc aatgagactc taggggtccag tggatgccac agcccagctt ggccctttcc 4208

ttccagatcc tgggtactga aagccttagg gaagctggcc tgagagggga agcgcccta 4268

agggagtgtc taagaacaaa agcgacccat tcagagactg tccctgaaac ctagtactgc 4328

cccccatgag gaaggaacag caatgggtgtc agtatccagg ctttgtacag agtgcttttc 4388

tgtttagttt ttactttttt tgttttgttt ttttaaagac gaaataaaga cccaggggag 4448

aatgggtggt gtatggggag gcaagtgtgg ggggtccttc tccacacca ctttgtccat 4508

ttgcaaatat attttggaac ac 4530

<210> 10

<211> 1255

<212> PRT

<213> Homo sapiens

<400> 10

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu  
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys  
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His  
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr  
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val  
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu



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85

90

95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr  
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro  
 115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser  
 130 135 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln  
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn  
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys  
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser  
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys  
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys  
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu  
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
 305 310 315 320

49321-137.ST25.txt

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys  
 325 330 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu  
 340 345 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys  
 355 360 365

Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp  
 370 375 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe  
 385 390 395 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro  
 405 410 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg  
 420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu  
 435 440 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly  
 450 455 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val  
 465 470 475 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr  
 485 490 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His  
 500 505 510

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys  
 515 520 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys  
 530 535 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys  
 545 550 555 560

## 49321-137.ST25.txt

Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys  
 565 570 575

Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp  
 580 585 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu  
 595 600 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln  
 610 615 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys  
 625 630 635 640

Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Val Ser  
 645 650 655

Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly  
 660 665 670

Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg  
 675 680 685

Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly  
 690 695 700

Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu  
 705 710 715 720

Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys  
 725 730 735

Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile  
 740 745 750

Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu  
 755 760 765

Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg  
 770 775 780

Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu  
 785 790 795 800

49321-137.ST25.txt

Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg  
805 810 815

Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly  
820 825 830

Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala  
835 840 845

Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe  
850 855 860

Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp  
865 870 875 880

Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg  
885 890 895

Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val  
900 905 910

Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala  
915 920 925

Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro  
930 935 940

Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met  
945 950 955 960

Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe  
965 970 975

Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu  
980 985 990

Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu  
995 1000 1005

Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr  
1010 1015 1020

Leu Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly

## 49321-137.ST25.txt

1025		1030		1035
Ala Gly Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg				
1040		1045		1050
Ser Gly Gly Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu				
1055		1060		1065
Glu Ala Pro Arg Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser				
1070		1075		1080
Asp Val Phe Asp Gly Asp Leu Gly Met Gly Ala Ala Lys Gly Leu				
1085		1090		1095
Gln Ser Leu Pro Thr His Asp Pro Ser Pro Leu Gln Arg Tyr Ser				
1100		1105		1110
Glu Asp Pro Thr Val Pro Leu Pro Ser Glu Thr Asp Gly Tyr Val				
1115		1120		1125
Ala Pro Leu Thr Cys Ser Pro Gln Pro Glu Tyr Val Asn Gln Pro				
1130		1135		1140
Asp Val Arg Pro Gln Pro Pro Ser Pro Arg Glu Gly Pro Leu Pro				
1145		1150		1155
Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu Arg Ala Lys Thr Leu				
1160		1165		1170
Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val Phe Ala Phe Gly				
1175		1180		1185
Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln Gly Gly Ala				
1190		1195		1200
Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala Phe Asp				
1205		1210		1215
Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala Pro				
1220		1225		1230
Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr				
1235		1240		1245

49321-137.ST25.txt

Leu Gly Leu Asp Val Pro Val  
1250 1255

<210> 11  
<211> 4975  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (199)..(4227)

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ttgcaatttg caacctccgc tgccgtcgcc gcagcagcca ccaattcgcc agcggttcag 120  
gtggctcttg cctcgatgtc ctagcctagg ggcccccggg ccggacttgg ctgggctccc 180  
ttcaccctct gcggagtc atg agg gcg aac gac gct ctg cag gtg ctg ggc 231  
Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly  
1 5 10  
ttg ctt ttc agc ctg gcc cgg ggc tcc gag gtg ggc aac tct cag gca 279  
Leu Leu Phe Ser Leu Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala  
15 20 25  
gtg tgt cct ggg act ctg aat ggc ctg agt gtg acc ggc gat gct gag 327  
Val Cys Pro Gly Thr Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu  
30 35 40  
aac caa tac cag aca ctg tac aag ctc tac gag agg tgt gag gtg gtg 375  
Asn Gln Tyr Gln Thr Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val  
45 50 55  
atg ggg aac ctt gag att gtg ctc acg gga cac aat gcc gac ctc tcc 423  
Met Gly Asn Leu Glu Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser  
60 65 70 75  
ttc ctg cag tgg att cga gaa gtg aca ggc tat gtc ctc gtg gcc atg 471  
Phe Leu Gln Trp Ile Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met  
80 85 90  
aat gaa ttc tct act cta cca ttg ccc aac ctc cgc gtg gtg cga ggg 519  
Asn Glu Phe Ser Thr Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly  
95 100 105  
acc cag gtc tac gat ggg aag ttt gcc atc ttc gtc atg ttg aac tat 567  
Thr Gln Val Tyr Asp Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr  
110 115 120  
aac acc aac tcc agc cac gct ctg cgc cag ctc cgc ttg act cag ctc 615  
Asn Thr Asn Ser Ser His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu  
125 130 135  
acc gag att ctg tca ggg ggt gtt tat att gag aag aac gat aag ctt 663  
Thr Glu Ile Leu Ser Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu

## 49321-137.ST25.txt

140	145	150	155	
tgt cac atg gac aca att gac tgg agg gac atc gtg agg gac cga gat				711
Cys His Met Asp Thr Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp	160	165	170	
gct gag ata gtg gtg aag gac aat ggc aga agc tgt ccc ccc tgt cat				759
Ala Glu Ile Val Val Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His	175	180	185	
gag gtt tgc aag ggg cga tgc tgg ggt cct gga tca gaa gac tgc cag				807
Glu Val Cys Lys Gly Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln	190	195	200	
aca ttg acc aag acc atc tgt gct cct cag tgt aat ggt cac tgc ttt				855
Thr Leu Thr Lys Thr Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe	205	210	215	
ggg ccc aac ccc aac cag tgc tgc cat gat gag tgt gcc ggg ggc tgc				903
Gly Pro Asn Pro Asn Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys	220	225	230	235
tca ggc cct cag gac aca gac tgc ttt gcc tgc cgg cac ttc aat gac				951
Ser Gly Pro Gln Asp Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp	240	245	250	
agt gga gcc tgt gta cct cgc tgt cca cag cct ctt gtc tac aac aag				999
Ser Gly Ala Cys Val Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys	255	260	265	
cta act ttc cag ctg gaa ccc aat ccc cac acc aag tat cag tat gga				1047
Leu Thr Phe Gln Leu Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly	270	275	280	
gga gtt tgt gta gcc agc tgt ccc cat aac ttt gtg gtg gat caa aca				1095
Gly Val Cys Val Ala Ser Cys Pro His Asn Phe Val Val Asp Gln Thr	285	290	295	
tcc tgt gtc agg gcc tgt cct cct gac aag atg gaa gta gat aaa aat				1143
Ser Cys Val Arg Ala Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn	300	305	310	315
ggg ctc aag atg tgt gag cct tgt ggg gga cta tgt ccc aaa gcc tgt				1191
Gly Leu Lys Met Cys Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys	320	325	330	
gag gga aca ggc tct ggg agc cgc ttc cag act gtg gac tcg agc aac				1239
Glu Gly Thr Gly Ser Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn	335	340	345	
att gat gga ttt gtg aac tgc acc aag atc ctg ggc aac ctg gac ttt				1287
Ile Asp Gly Phe Val Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe	350	355	360	
ctg atc acc ggc ctc aat gga gac ccc tgg cac aag atc cct gcc ctg				1335
Leu Ile Thr Gly Leu Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu	365	370	375	
gac cca gag aag ctc aat gtc ttc cgg aca gta cgg gag atc aca ggt				1383

## 49321-137.ST25.txt

Asp 380	Pro	Glu	Lys	Leu	Asn 385	Val	Phe	Arg	Thr	Val 390	Arg	Glu	Ile	Thr	Gly 395	
tac	ctg	aac	atc	cag	tcc	tgg	ccg	ccc	cac	atg	cac	aac	ttc	agt	gtt	1431
Tyr	Leu	Asn	Ile	Gln	Ser	Trp	Pro	Pro	His	Met	His	Asn	Phe	Ser	Val	
				400					405				410			
ttt	tcc	aat	ttg	aca	acc	att	gga	ggc	aga	agc	ctc	tac	aac	cgg	ggc	1479
Phe	Ser	Asn	Leu	Thr	Thr	Ile	Gly	Gly	Arg	Ser	Leu	Tyr	Asn	Arg	Gly	
			415					420					425			
ttc	tca	ttg	ttg	atc	atg	aag	aac	ttg	aat	gtc	aca	tct	ctg	ggc	ttc	1527
Phe	Ser	Leu	Leu	Ile	Met	Lys	Asn	Leu	Asn	Val	Thr	Ser	Leu	Gly	Phe	
		430					435					440				
cga	tcc	ctg	aag	gaa	att	agt	gct	ggg	cgt	atc	tat	ata	agt	gcc	aat	1575
Arg	Ser	Leu	Lys	Glu	Ile	Ser	Ala	Gly	Arg	Ile	Tyr	Ile	Ser	Ala	Asn	
	445					450					455					
agg	cag	ctc	tgc	tac	cac	cac	tct	ttg	aac	tgg	acc	aag	gtg	ctt	cgg	1623
Arg	Gln	Leu	Cys	Tyr	His	His	Ser	Leu	Asn	Trp	Thr	Lys	Val	Leu	Arg	
460					465					470					475	
ggg	cct	acg	gaa	gag	cga	cta	gac	atc	aag	cat	aat	cgg	ccg	cgc	aga	1671
Gly	Pro	Thr	Glu	Glu	Arg	Leu	Asp	Ile	Lys	His	Asn	Arg	Pro	Arg	Arg	
			480						485					490		
gac	tgc	gtg	gca	gag	ggc	aaa	gtg	tgt	gac	cca	ctg	tgc	tcc	tct	ggg	1719
Asp	Cys	Val	Ala	Glu	Gly	Lys	Val	Cys	Asp	Pro	Leu	Cys	Ser	Ser	Gly	
		495					500					505				
gga	tgc	tgg	ggc	cca	ggc	cct	ggt	cag	tgc	ttg	tcc	tgt	cga	aat	tat	1767
Gly	Cys	Trp	Gly	Pro	Gly	Pro	Gly	Gln	Cys	Leu	Ser	Cys	Arg	Asn	Tyr	
	510					515						520				
agc	cga	gga	ggt	gtc	tgt	gtg	acc	cac	tgc	aac	ttt	ctg	aat	ggg	gag	1815
Ser	Arg	Gly	Gly	Val	Cys	Val	Thr	His	Cys	Asn	Phe	Leu	Asn	Gly	Glu	
	525					530					535					
cct	cga	gaa	ttt	gcc	cat	gag	gcc	gaa	tgc	ttc	tcc	tgc	cac	ccg	gaa	1863
Pro	Arg	Glu	Phe	Ala	His	Glu	Ala	Glu	Cys	Phe	Ser	Cys	His	Pro	Glu	
540				545					550						555	
tgc	caa	ccc	atg	ggg	ggc	act	gcc	aca	tgc	aat	ggc	tcg	ggc	tct	gat	1911
Cys	Gln	Pro	Met	Gly	Gly	Thr	Ala	Thr	Cys	Asn	Gly	Ser	Gly	Ser	Asp	
			560					565					570			
act	tgt	gct	caa	tgt	gcc	cat	ttt	cga	gat	ggg	ccc	cac	tgt	gtg	agc	1959
Thr	Cys	Ala	Gln	Cys	Ala	His	Phe	Arg	Asp	Gly	Pro	His	Cys	Val	Ser	
		575						580				585				
agc	tgc	ccc	cat	gga	gtc	cta	ggt	gcc	aag	ggc	cca	atc	tac	aag	tac	2007
Ser	Cys	Pro	His	Gly	Val	Leu	Gly	Ala	Lys	Gly	Pro	Ile	Tyr	Lys	Tyr	
	590						595					600				
cca	gat	gtt	cag	aat	gaa	tgt	cgg	ccc	tgc	cat	gag	aac	tgc	acc	cag	2055
Pro	Asp	Val	Gln	Asn	Glu	Cys	Arg	Pro	Cys	His	Glu	Asn	Cys	Thr	Gln	
	605					610					615					



## 49321-137.ST25.txt

ggg tgt aaa gga cca gag ctt caa gac tgt tta gga caa aca ctg gtg Gly Cys Lys Gly Pro Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val 620 625 630 635	2103
ctg atc ggc aaa acc cat ctg aca atg gct ttg aca gtg ata gca gga Leu Ile Gly Lys Thr His Leu Thr Met Ala Leu Thr Val Ile Ala Gly 640 645 650	2151
ttg gta gtg att ttc atg atg ctg ggc ggc act ttt ctc tac tgg cgt Leu Val Val Ile Phe Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg 655 660 665	2199
ggg cgc cgg att cag aat aaa agg gct atg agg cga tac ttg gaa cgg Gly Arg Arg Ile Gln Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg 670 675 680	2247
ggt gag agc ata gag cct ctg gac ccc agt gag aag gct aac aaa gtc Gly Glu Ser Ile Glu Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val 685 690 695	2295
ttg gcc aga atc ttc aaa gag aca gag cta agg aag ctt aaa gtg ctt Leu Ala Arg Ile Phe Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu 700 705 710 715	2343
ggc tcg ggt gtc ttt gga act gtg cac aaa gga gtg tgg atc cct gag Gly Ser Gly Val Phe Gly Thr Val His Lys Gly Val Trp Ile Pro Glu 720 725 730	2391
ggt gaa tca atc aag att cca gtc tgc att aaa gtc att gag gac aag Gly Glu Ser Ile Lys Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys 735 740 745	2439
agt gga cgg cag agt ttt caa gct gtg aca gat cat atg ctg gcc att Ser Gly Arg Gln Ser Phe Gln Ala Val Thr Asp His Met Leu Ala Ile 750 755 760	2487
ggc agc ctg gac cat gcc cac att gta agg ctg ctg gga cta tgc cca Gly Ser Leu Asp His Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro 765 770 775	2535
ggg tca tct ctg cag ctt gtc act caa tat ttg cct ctg ggt tct ctg Gly Ser Ser Leu Gln Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu 780 785 790 795	2583
ctg gat cat gtg aga caa cac cgg ggg gca ctg ggg cca cag ctg ctg Leu Asp His Val Arg Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu 800 805 810	2631
ctc aac tgg gga gta caa att gcc aag gga atg tac tac ctt gag gaa Leu Asn Trp Gly Val Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu 815 820 825	2679
cat ggt atg gtg cat aga aac ctg gct gcc cga aac gtg cta ctc aag His Gly Met Val His Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys 830 835 840	2727
tca ccc agt cag gtt cag gtg gca gat ttt ggt gtg gct gac ctg ctg Ser Pro Ser Gln Val Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu 845 850 855	2775

## 49321-137.ST25.txt

cct cct gat gat aag cag ctg cta tac agt gag gcc aag act cca att	2823
Pro Pro Asp Asp Lys Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile	
860 865 870 875	
aag tgg atg gcc ctt gag agt atc cac ttt ggg aaa tac aca cac cag	2871
Lys Trp Met Ala Leu Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln	
880 885 890	
agt gat gtc tgg agc tat ggt gtg aca gtt tgg gag ttg atg acc ttc	2919
Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe	
895 900 905	
ggg gca gag ccc tat gca ggg cta cga ttg gct gaa gta cca gac ctg	2967
Gly Ala Glu Pro Tyr Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu	
910 915 920	
cta gag aag ggg gag cgg ttg gca cag ccc cag atc tgc aca att gat	3015
Leu Glu Lys Gly Glu Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp	
925 930 935	
gtc tac atg gtg atg gtc aag tgt tgg atg att gat gag aac att cgc	3063
Val Tyr Met Val Met Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg	
940 945 950 955	
cca acc ttt aaa gaa cta gcc aat gag ttc acc agg atg gcc cga gac	3111
Pro Thr Phe Lys Glu Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp	
960 965 970	
cca cca cgg tat ctg gtc ata aag aga gag agt ggg cct gga ata gcc	3159
Pro Pro Arg Tyr Leu Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala	
975 980 985	
cct ggg cca gag ccc cat ggt ctg aca aac aag aag cta gag gaa gta	3207
Pro Gly Pro Glu Pro His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val	
990 995 1000	
gag ctg gag cca gaa cta gac cta gac cta gac ttg gaa gca gag	3252
Glu Leu Glu Pro Glu Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu	
1005 1010 1015	
gag gac aac ctg gca acc acc aca ctg ggc tcc gcc ctc agc cta	3297
Glu Asp Asn Leu Ala Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu	
1020 1025 1030	
cca gtt gga aca ctt aat cgg cca cgt ggg agc cag agc ctt tta	3342
Pro Val Gly Thr Leu Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu	
1035 1040 1045	
agt cca tca tct gga tac atg ccc atg aac cag ggt aat ctt ggg	3387
Ser Pro Ser Ser Gly Tyr Met Pro Met Asn Gln Gly Asn Leu Gly	
1050 1055 1060	
ggg tct tgc cag gag tct gca gtt tct ggg agc agt gaa cgg tgc	3432
Gly Ser Cys Gln Glu Ser Ala Val Ser Gly Ser Ser Glu Arg Cys	
1065 1070 1075	
ccc cgt cca gtc tct cta cac cca atg cca cgg gga tgc ctg gca	3477
Pro Arg Pro Val Ser Leu His Pro Met Pro Arg Gly Cys Leu Ala	

## 49321-137.ST25.txt

1080		1085		1090		
tca gag Ser Glu 1095	tca tca gag ggg Ser Ser Glu Gly 1100	cat His 1100	gta aca ggc tct Val Thr Gly Ser 1105	gag Glu 1105	gct gag ctc Ala Glu Leu 1110	3522
cag gag Gln Glu 1110	aaa gtg tca atg Lys Val Ser Met 1115	tgt Cys 1115	aga agc cgg agc Arg Ser Arg Ser 1120	agg Arg 1120	agc cgg agc Ser Arg Ser 1125	3567
cca cgg Pro Arg 1125	cca cgc gga gat Pro Arg Gly Asp 1130	agc Ser 1130	gcc tac cat tcc Ala Tyr His Ser 1135	cag Gln 1135	cgc cac agt Arg His Ser 1140	3612
ctg ctg Leu Leu 1140	act cct gtt acc Thr Pro Val Thr 1145	cca Pro 1145	ctc tcc cca ccc Leu Ser Pro Pro 1150	ggg Gly 1150	tta gag gaa Leu Glu Glu 1155	3657
gag gat Glu Asp 1155	gtc aac ggt tat Val Asn Gly Tyr 1160	gtc Val 1160	atg cca gat aca Met Pro Asp Thr 1165	cac His 1165	ctc aaa ggt Leu Lys Gly 1170	3702
act ccc Thr Pro 1170	tcc tcc cgg gaa Ser Ser Arg Glu 1175	ggc Gly 1175	acc ctt tct tca Thr Leu Ser Ser 1180	gtg Val 1180	ggg ctc agt Gly Leu Ser 1185	3747
tct gtc Ser Val 1185	ctg ggt act gaa Leu Gly Thr Glu 1190	gaa Glu 1190	gaa gat gaa gat Glu Asp Glu Asp 1195	gag Glu 1195	gag tat gaa Glu Tyr Glu 1200	3792
tac atg Tyr Met 1200	aac cgg agg aga Asn Arg Arg Arg 1205	agg Arg 1205	cac agt cca cct His Ser Pro Pro 1210	cat His 1210	ccc cct agg Pro Pro Arg 1215	3837
cca agt Pro Ser 1215	tcc ctt gag gag Ser Leu Glu Glu 1220	ctg Leu 1220	ggg tat gag tac Gly Tyr Glu Tyr 1225	atg Met 1225	gat gtg ggg Asp Val Gly 1230	3882
tca gac Ser Asp 1230	ctc agt gcc tct Leu Ser Ala Ser 1235	ctg Leu 1235	ggc agc aca cag Gly Ser Thr Gln 1240	agt Ser 1240	tgc cca ctc Cys Pro Leu 1245	3927
cac cct His Pro 1245	gta ccc atc atg Val Pro Ile Met 1250	ccc Pro 1250	act gca ggc aca Thr Ala Gly Thr 1255	act Thr 1255	cca gat gaa Pro Asp Glu 1260	3972
gac tat Asp Tyr 1260	gaa tat atg aat Glu Tyr Met Asn 1265	cgg Arg 1265	caa cga gat gga Gln Arg Asp Gly 1270	ggg Gly 1270	ggg cct ggg Gly Pro Gly 1275	4017
ggg gat Gly Asp 1275	tat gca gcc atg Tyr Ala Ala Met 1280	ggg Gly 1280	gcc tgc cca gca Ala Cys Pro Ala 1285	tct Ser 1285	gag caa ggg Glu Gln Gly 1290	4062
tat gaa Tyr Glu 1290	gag atg aga gct Glu Met Arg Ala 1295	ttt Phe 1295	cag ggg cct gga Gln Gly Pro Gly 1300	cat His 1300	cag gcc ccc Gln Ala Pro 1305	4107
cat gtc cat 1310	cat tat gcc cgc cat 1315	cta aaa 1315	aaa act cta cgt aaa 1320	agc agg 1320	tta gag gct agg 1325	4152

## 49321-137.ST25.txt

His Val His Tyr Ala Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala  
 1305 1310 1315

aca gac tct gcc ttt gat aac cct gat tac tgg cat agc agg ctt 4197  
 Thr Asp Ser Ala Phe Asp Asn Pro Asp Tyr Trp His Ser Arg Leu  
 1320 1325 1330

ttc ccc aag gct aat gcc cag aga acg taa ctctgctcc ctgtggcact 4247  
 Phe Pro Lys Ala Asn Ala Gln Arg Thr  
 1335 1340

caggagcat ttaatggcag ctagtgcctt tagagggtac cgtcttctcc ctattccctc 4307

tctctcccag gtcccagccc cttttcccca gtcccagaca attccattca atctttggag 4367

gcttttaaac attttgacac aaaattctta tggatgtag ccagctgtgc actttcttct 4427

ctttcccaac ccagggaaag gttttcctta ttttgtgtgc tttccagtc ccattcctca 4487

gcttcttcac aggcactcct ggagatatga aggattactc tccatatccc ttcctctcag 4547

gctcttgact acttggaaact aggctcttat gtgtgccttt gtttcccatc agactgtcaa 4607

gaagaggaaa gggaggaaac ctagcagagg aaagtgtaat tttggtttat gactcttaac 4667

cccctagaaa gacagaagct taaaatctgt gaagaaagag gttaggagta gatattgatt 4727

actatcataa ttcagcactt aactatgagc caggcatcat actaaacttc acctacatta 4787

tctcacttag tcctttatca tccttaaaac aattctgtga catacatatt atctcatttt 4847

acacaaaggg aagtcgggca tgggtggctca tgctgtaat ctgagcactt tgggaggctg 4907

aggcagaagg attacctgag gcaaggagtt tgagaccagc tttagccaaca tagtaagacc 4967

cccatctc 4975

<210> 12  
 <211> 1342  
 <212> PRT  
 <213> Homo sapiens  
 <400> 12

Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly Leu Leu Phe Ser Leu  
 1 5 10 15

Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala Val Cys Pro Gly Thr  
 20 25 30

Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu Asn Gln Tyr Gln Thr  
 35 40 45

Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val Met Gly Asn Leu Glu  
 50 55 60

49321-137.ST25.txt

Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile  
65 70 75 80

Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Thr  
85 90 95

Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp  
100 105 110

Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser  
115 120 125

His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu Thr Glu Ile Leu Ser  
130 135 140

Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr  
145 150 155 160

Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp Ala Glu Ile Val Val  
165 170 175

Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His Glu Val Cys Lys Gly  
180 185 190

Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln Thr Leu Thr Lys Thr  
195 200 205

Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe Gly Pro Asn Pro Asn  
210 215 220

Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp  
225 230 235 240

Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp Ser Gly Ala Cys Val  
245 250 255

Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu  
260 265 270

Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala  
275 280 285

Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Ser Cys Val Arg Ala

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290

295

300

Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys  
 305 310 315 320

Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys Glu Gly Thr Gly Ser  
 325 330 335

Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn Ile Asp Gly Phe Val  
 340 345 350

Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gly Leu  
 355 360 365

Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu Asp Pro Glu Lys Leu  
 370 375 380

Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly Tyr Leu Asn Ile Gln  
 385 390 395 400

Ser Trp Pro Pro His Met His Asn Phe Ser Val Phe Ser Asn Leu Thr  
 405 410 415

Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu Ile  
 420 425 430

Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe Arg Ser Leu Lys Glu  
 435 440 445

Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn Arg Gln Leu Cys Tyr  
 450 455 460

His His Ser Leu Asn Trp Thr Lys Val Leu Arg Gly Pro Thr Glu Glu  
 465 470 475 480

Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg Asp Cys Val Ala Glu  
 485 490 495

Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly Pro  
 500 505 510

Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr Ser Arg Gly Gly Val  
 515 520 525

## 49321-137.ST25.txt

Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu Pro Arg Glu Phe Ala  
 530 535 540

His Glu Ala Glu Cys Phe Ser Cys His Pro Glu Cys Gln Pro Met Gly  
 545 550 555 560

Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp Thr Cys Ala Gln Cys  
 565 570 575

Ala His Phe Arg Asp Gly Pro His Cys Val Ser Ser Cys Pro His Gly  
 580 585 590

Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr Pro Asp Val Gln Asn  
 595 600 605

Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln Gly Cys Lys Gly Pro  
 610 615 620

Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val Leu Ile Gly Lys Thr  
 625 630 635 640

His Leu Thr Met Ala Leu Thr Val Ile Ala Gly Leu Val Val Ile Phe  
 645 650 655

Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile Gln  
 660 665 670

Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg Gly Glu Ser Ile Glu  
 675 680 685

Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val Leu Ala Arg Ile Phe  
 690 695 700

Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Val Phe  
 705 710 715 720

Gly Thr Val His Lys Gly Val Trp Ile Pro Glu Gly Glu Ser Ile Lys  
 725 730 735

Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys Ser Gly Arg Gln Ser  
 740 745 750

Phe Gln Ala Val Thr Asp His Met Leu Ala Ile Gly Ser Leu Asp His  
 755 760 765

## 49321-137.ST25.txt

Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro Gly Ser Ser Leu Gln  
 770 775 780

Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu Leu Asp His Val Arg  
 785 790 795 800

Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu Leu Asn Trp Gly Val  
 805 810 815

Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu His Gly Met Val His  
 820 825 830

Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys Ser Pro Ser Gln Val  
 835 840 845

Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu Pro Pro Asp Asp Lys  
 850 855 860

Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile Lys Trp Met Ala Leu  
 865 870 875 880

Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln Ser Asp Val Trp Ser  
 885 890 895

Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala Glu Pro Tyr  
 900 905 910

Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu Leu Glu Lys Gly Glu  
 915 920 925

Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr Met Val Met  
 930 935 940

Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg Pro Thr Phe Lys Glu  
 945 950 955 960

Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp Pro Pro Arg Tyr Leu  
 965 970 975

Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu Pro  
 980 985 990

His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val Glu Leu Glu Pro Glu  
 995 1000 1005



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Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu Glu Asp Asn Leu Ala  
 1010 1015 1020  
 Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu Pro Val Gly Thr Leu  
 1025 1030 1035  
 Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu Ser Pro Ser Ser Gly  
 1040 1045 1050  
 Tyr Met Pro Met Asn Gln Gly Asn Leu Gly Gly Ser Cys Gln Glu  
 1055 1060 1065  
 Ser Ala Val Ser Gly Ser Ser Glu Arg Cys Pro Arg Pro Val Ser  
 1070 1075 1080  
 Leu His Pro Met Pro Arg Gly Cys Leu Ala Ser Glu Ser Ser Glu  
 1085 1090 1095  
 Gly His Val Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser  
 1100 1105 1110  
 Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly  
 1115 1120 1125  
 Asp Ser Ala Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val  
 1130 1135 1140  
 Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu Glu Asp Val Asn Gly  
 1145 1150 1155  
 Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg  
 1160 1165 1170  
 Glu Gly Thr Leu Ser Ser Val Gly Leu Ser Ser Val Leu Gly Thr  
 1175 1180 1185  
 Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Arg  
 1190 1195 1200  
 Arg Arg His Ser Pro Pro His Pro Pro Arg Pro Ser Ser Leu Glu  
 1205 1210 1215  
 Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu Ser Ala

## 49321-137.ST25.txt

1220

1225

1230

Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile  
 1235 1240 1245

Met Pro Thr Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu Tyr Met  
 1250 1255 1260

Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly Gly Asp Tyr Ala Ala  
 1265 1270 1275

Met Gly Ala Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu Met Arg  
 1280 1285 1290

Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala  
 1295 1300 1305

Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala Thr Asp Ser Ala Phe  
 1310 1315 1320

Asp Asn Pro Asp Tyr Trp His Ser Arg Leu Phe Pro Lys Ala Asn  
 1325 1330 1335

Ala Gln Arg Thr  
 1340

<210> 13  
 <211> 4975  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (199)..(4227)  
 <223> HER-3 mutant coding sequence

<220>  
 <221> mutation  
 <222> (1877)..(1877)  
 <223> mutation, comprising substitution of "a" instead of "g" at this position

<400> 13  
 ctctcacaca cacacacccc tccctgcca tccctccccg gactccgggt ccggctccga 60  
 ttgcaatttg caacctccgc tgccgtcgcc gcagcagcca ccaattcgcc agcgggttcag 120  
 gtggctcttg cctcgatgtc ctagcctagg ggcccccggg ccggacttgg ctggggtccc 180

49321-137.ST25.txt

ttcacccctct gcggagtc atg agg gcg aac gac gct ctg cag gtg ctg ggc	231
Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly	
1 5 10	
ttg ctt ttc agc ctg gcc cgg ggc tcc gag gtg ggc aac tct cag gca	279
Leu Leu Phe Ser Leu Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala	
15 20 25	
gtg tgt cct ggg act ctg aat ggc ctg agt gtg acc ggc gat gct gag	327
Val Cys Pro Gly Thr Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu	
30 35 40	
aac caa tac cag aca ctg tac aag ctc tac gag agg tgt gag gtg gtg	375
Asn Gln Tyr Gln Thr Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val	
45 50 55	
atg ggg aac ctt gag att gtg ctc acg gga cac aat gcc gac ctc tcc	423
Met Gly Asn Leu Glu Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser	
60 65 70 75	
ttc ctg cag tgg att cga gaa gtg aca ggc tat gtc ctc gtg gcc atg	471
Phe Leu Gln Trp Ile Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met	
80 85 90	
aat gaa ttc tct act cta cca ttg ccc aac ctc cgc gtg gtg cga ggg	519
Asn Glu Phe Ser Thr Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly	
95 100 105	
acc cag gtc tac gat ggg aag ttt gcc atc ttc gtc atg ttg aac tat	567
Thr Gln Val Tyr Asp Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr	
110 115 120	
aac acc aac tcc agc cac gct ctg cgc cag ctc cgc ttg act cag ctc	615
Asn Thr Asn Ser Ser His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu	
125 130 135	
acc gag att ctg tca ggg ggt gtt tat att gag aag aac gat aag ctt	663
Thr Glu Ile Leu Ser Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu	
140 145 150 155	
tgt cac atg gac aca att gac tgg agg gac atc gtg agg gac cga gat	711
Cys His Met Asp Thr Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp	
160 165 170	
gct gag ata gtg gtg aag gac aat ggc aga agc tgt ccc ccc tgt cat	759
Ala Glu Ile Val Val Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His	
175 180 185	
gag gtt tgc aag ggg cga tgc tgg ggt cct gga tca gaa gac tgc cag	807
Glu Val Cys Lys Gly Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln	
190 195 200	
aca ttg acc aag acc atc tgt gct cct cag tgt aat ggt cac tgc ttt	855
Thr Leu Thr Lys Thr Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe	
205 210 215	
ggg ccc aac ccc aac cag tgc tgc cat gat gag tgt gcc ggg ggc tgc	903
Gly Pro Asn Pro Asn Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys	
220 225 230 235	

## 49321-137.ST25.txt

tca ggc cct cag gac aca gac tgc ttt gcc tgc cgg cac ttc aat gac Ser Gly Pro Gln Asp Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp 240 245 250	951
agt gga gcc tgt gta cct cgc tgt cca cag cct ctt gtc tac aac aag Ser Gly Ala Cys Val Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys 255 260 265	999
cta act ttc cag ctg gaa ccc aat ccc cac acc aag tat cag tat gga Leu Thr Phe Gln Leu Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly 270 275 280	1047
gga gtt tgt gta gcc agc tgt ccc cat aac ttt gtg gtg gat caa aca Gly Val Cys Val Ala Ser Cys Pro His Asn Phe Val Val Asp Gln Thr 285 290 295	1095
tcc tgt gtc agg gcc tgt cct cct gac aag atg gaa gta gat aaa aat Ser Cys Val Arg Ala Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn 300 305 310 315	1143
ggg ctc aag atg tgt gag cct tgt ggg gga cta tgt ccc aaa gcc tgt Gly Leu Lys Met Cys Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys 320 325 330	1191
gag gga aca ggc tct ggg agc cgc ttc cag act gtg gac tcg agc aac Glu Gly Thr Gly Ser Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn 335 340 345	1239
att gat gga ttt gtg aac tgc acc aag atc ctg ggc aac ctg gac ttt Ile Asp Gly Phe Val Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe 350 355 360	1287
ctg atc acc ggc ctc aat gga gac ccc tgg cac aag atc cct gcc ctg Leu Ile Thr Gly Leu Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu 365 370 375	1335
gac cca gag aag ctc aat gtc ttc cgg aca gta cgg gag atc aca ggt Asp Pro Glu Lys Leu Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly 380 385 390 395	1383
tac ctg aac atc cag tcc tgg ccg ccc cac atg cac aac ttc agt gtt Tyr Leu Asn Ile Gln Ser Trp Pro Pro His Met His Asn Phe Ser Val 400 405 410	1431
ttt tcc aat ttg aca acc att gga ggc aga agc ctc tac aac cgg ggc Phe Ser Asn Leu Thr Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly 415 420 425	1479
ttc tca ttg ttg atc atg aag aac ttg aat gtc aca tct ctg ggc ttc Phe Ser Leu Leu Ile Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe 430 435 440	1527
cga tcc ctg aag gaa att agt gct ggg cgt atc tat ata agt gcc aat Arg Ser Leu Lys Glu Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn 445 450 455	1575
agg cag ctc tgc tac cac cac tct ttg aac tgg acc aag gtg ctt cgg Arg Gln Leu Cys Tyr His His Ser Leu Asn Trp Thr Lys Val Leu Arg	1623

49321-137.ST25.txt

460	465	470	475	
ggg cct acg gaa gag cga cta gac atc aag cat aat cgg ccg cgc aga Gly Pro Thr Glu Glu Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg	480	485	490	1671
gac tgc gtg gca gag ggc aaa gtg tgt gac cca ctg tgc tcc tct ggg Asp Cys Val Ala Glu Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly	495	500	505	1719
gga tgc tgg ggc cca ggc cct ggt cag tgc ttg tcc tgt cga aat tat Gly Cys Trp Gly Pro Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr	510	515	520	1767
agc cga gga ggt gtc tgt gtg acc cac tgc aac ttt ctg aat ggg gag Ser Arg Gly Gly Val Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu	525	530	535	1815
cct cga gaa ttt gcc cat gag gcc gaa tgc ttc tcc tgc cac ccg gaa Pro Arg Glu Phe Ala His Glu Ala Glu Cys Phe Ser Cys His Pro Glu	540	545	550	1863
tgc caa ccc atg gag ggc act gcc aca tgc aat ggc tcg ggc tct gat Cys Gln Pro Met Glu Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp	560	565	570	1911
act tgt gct caa tgt gcc cat ttt cga gat ggg ccc cac tgt gtg agc Thr Cys Ala Gln Cys Ala His Phe Arg Asp Gly Pro His Cys Val Ser	575	580	585	1959
agc tgc ccc cat gga gtc cta ggt gcc aag ggc cca atc tac aag tac Ser Cys Pro His Gly Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr	590	595	600	2007
cca gat gtt cag aat gaa tgt cgg ccc tgc cat gag aac tgc acc cag Pro Asp Val Gln Asn Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln	605	610	615	2055
ggg tgt aaa gga cca gag ctt caa gac tgt tta gga caa aca ctg gtg Gly Cys Lys Gly Pro Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val	620	625	630	2103
ctg atc ggc aaa acc cat ctg aca atg gct ttg aca gtg ata gca gga Leu Ile Gly Lys Thr His Leu Thr Met Ala Leu Thr Val Ile Ala Gly	640	645	650	2151
ttg gta gtg att ttc atg atg ctg ggc ggc act ttt ctc tac tgg cgt Leu Val Val Ile Phe Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg	655	660	665	2199
ggg cgc cgg att cag aat aaa agg gct atg agg cga tac ttg gaa cgg Gly Arg Arg Ile Gln Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg	670	675	680	2247
ggt gag agc ata gag cct ctg gac ccc agt gag aag gct aac aaa gtc Gly Glu Ser Ile Glu Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val	685	690	695	2295
ttg gcc aga atc ttc aaa gag aca gag cta agg aag ctt aaa gtg ctt				2343

Leu 700	Ala	Arg	Ile	Phe	Lys 705	Glu	Thr	Glu	Leu	Arg 710	Lys	Leu	Lys	Val	Leu 715	
ggc Gly	tcg Ser	ggt Gly	gtc Val	ttt Phe 720	gga Gly	act Thr	gtg Val	cac His	aaa Lys 725	gga Gly	gtg Val	tgg Trp	atc Ile	cct Pro 730	gag Glu	2391
ggt Gly	gaa Glu	tca Ser	atc Ile 735	aag Lys	att Ile	cca Pro	gtc Val	tgc Cys 740	att Ile	aaa Lys	gtc Val	att Ile	gag Glu 745	gac Asp	aag Lys	2439
agt Ser	gga Gly	cgg Arg 750	cag Gln	agt Ser	ttt Phe	caa Gln	gct Ala 755	gtg Val	aca Thr	gat Asp	cat His	atg Met 760	ctg Leu	gcc Ala	att Ile	2487
ggc Gly	agc Ser 765	ctg Leu	gac Asp	cat His	gcc Ala 770	cac His	att Ile 775	gta Val	agg Arg	ctg Leu	ctg Leu 775	gga Gly	cta Leu	tgc Cys	cca Pro	2535
ggg Gly 780	tca Ser	tct Ser	ctg Leu	cag Gln 785	ctt Leu	gtc Val	act Thr	caa Gln	tat Tyr 790	ttg Leu	cct Pro	ctg Leu	ggt Gly	tct Ser	ctg Leu 795	2583
ctg Leu	gat Asp	cat His	gtg Val 800	aga Arg	caa Gln	cac His	cgg Arg	ggg Gly	gca Ala 805	ctg Leu	ggg Gly	cca Pro	cag Gln	ctg Leu 810	ctg Leu	2631
ctc Leu	aac Asn	tgg Trp 815	gga Gly	gta Val	caa Gln	att Ile	gcc Ala	aag Lys 820	gga Gly	atg Met	tac Tyr	tac Tyr	ctt Leu 825	gag Glu	gaa Glu	2679
cat His	ggt Gly 830	atg Met	gtg Val	cat His	aga Arg	aac Asn	ctg Leu 835	gct Ala	gcc Ala	cga Arg	aac Asn	gtg Val 840	cta Leu	ctc Leu	aag Lys	2727
tca Ser 845	ccc Pro	agt Ser	cag Gln	gtt Val	cag Gln	gtg Val	gca Ala 850	gat Asp	ttt Phe	ggt Gly	gtg Val 855	gct Ala	gac Asp	ctg Leu	ctg Leu	2775
cct Pro 860	cct Pro	gat Asp	gat Asp	aag Lys	cag Gln 865	ctg Leu	cta Leu	tac Tyr	agt Ser	gag Glu 870	gcc Ala	aag Lys	act Thr	cca Pro	att Ile 875	2823
aag Lys	tgg Trp	atg Met	gcc Ala 880	ctt Leu	gag Glu	agt Ser	atc Ile	cac His	ttt Phe 885	ggg Gly	aaa Lys	tac Tyr	aca Thr	cac His 890	cag Gln	2871
agt Ser	gat Asp	gtc Val 895	tgg Trp	agc Ser	tat Tyr	ggt Gly	gtg Val	aca Thr 900	gtt Val	tgg Trp	gag Glu	ttg Leu	atg Met 905	acc Thr	ttc Phe	2919
ggg Gly	gca Ala 910	gag Glu	ccc Pro	tat Tyr	gca Ala	ggg Gly	cta Leu 915	cga Arg	ttg Leu	gct Ala	gaa Glu	gta Val 920	cca Pro	gac Asp	ctg Leu	2967
cta Leu 925	gag Glu	aag Lys	ggg Gly	gag Glu	cgg Arg	ttg Leu 930	gca Ala	cag Gln	ccc Pro	cag Gln	atc Ile 935	tgc Cys	aca Thr	att Ile	gat Asp	3015

## 49321-137.ST25.txt

gtc tac atg gtg atg gtc aag tgt tgg atg att gat gag aac att cgc	3063
Val Tyr Met Val Met Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg	
940 945 950 955	
cca acc ttt aaa gaa cta gcc aat gag ttc acc agg atg gcc cga gac	3111
Pro Thr Phe Lys Glu Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp	
960 965 970	
cca cca cgg tat ctg gtc ata aag aga gag agt ggg cct gga ata gcc	3159
Pro Pro Arg Tyr Leu Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala	
975 980 985	
cct ggg cca gag ccc cat ggt ctg aca aac aag aag cta gag gaa gta	3207
Pro Gly Pro Glu Pro His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val	
990 995 1000	
gag ctg gag cca gaa cta gac cta gac cta gac ttg gaa gca gag	3252
Glu Leu Glu Pro Glu Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu	
1005 1010 1015	
gag gac aac ctg gca acc acc aca ctg ggc tcc gcc ctc agc cta	3297
Glu Asp Asn Leu Ala Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu	
1020 1025 1030	
cca gtt gga aca ctt aat cgg cca cgt ggg agc cag agc ctt tta	3342
Pro Val Gly Thr Leu Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu	
1035 1040 1045	
agt cca tca tct gga tac atg ccc atg aac cag ggt aat ctt ggg	3387
Ser Pro Ser Ser Gly Tyr Met Pro Met Asn Gln Gly Asn Leu Gly	
1050 1055 1060	
ggg tct tgc cag gag tct gca gtt tct ggg agc agt gaa cgg tgc	3432
Gly Ser Cys Gln Glu Ser Ala Val Ser Gly Ser Ser Glu Arg Cys	
1065 1070 1075	
ccc cgt cca gtc tct cta cac cca atg cca cgg gga tgc ctg gca	3477
Pro Arg Pro Val Ser Leu His Pro Met Pro Arg Gly Cys Leu Ala	
1080 1085 1090	
tca gag tca tca gag ggg cat gta aca ggc tct gag gct gag ctc	3522
Ser Glu Ser Ser Glu Gly His Val Thr Gly Ser Glu Ala Glu Leu	
1095 1100 1105	
cag gag aaa gtg tca atg tgt aga agc cgg agc agg agc cgg agc	3567
Gln Glu Lys Val Ser Met Cys Arg Ser Arg Ser Arg Ser Arg Ser	
1110 1115 1120	
cca cgg cca cgc gga gat agc gcc tac cat tcc cag cgc cac agt	3612
Pro Arg Pro Arg Gly Asp Ser Ala Tyr His Ser Gln Arg His Ser	
1125 1130 1135	
ctg ctg act cct gtt acc cca ctc tcc cca ccc ggg tta gag gaa	3657
Leu Leu Thr Pro Val Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu	
1140 1145 1150	
gag gat gtc aac ggt tat gtc atg cca gat aca cac ctc aaa ggt	3702
Glu Asp Val Asn Gly Tyr Val Met Pro Asp Thr His Leu Lys Gly	
1155 1160 1165	

## 49321-137.ST25.txt

act ccc tcc tcc cgg gaa ggc acc ctt tct tca gtg ggt ctc agt	3747
Thr Pro Ser Ser Arg Glu Gly Thr Leu Ser Ser Val Gly Leu Ser	
1170 1175 1180	
tct gtc ctg ggt act gaa gaa gaa gat gaa gat gag gag tat gaa	3792
Ser Val Leu Gly Thr Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu	
1185 1190 1195	
tac atg aac cgg agg aga agg cac agt cca cct cat ccc cct agg	3837
Tyr Met Asn Arg Arg Arg Arg His Ser Pro Pro His Pro Pro Arg	
1200 1205 1210	
cca agt tcc ctt gag gag ctg ggt tat gag tac atg gat gtg ggg	3882
Pro Ser Ser Leu Glu Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly	
1215 1220 1225	
tca gac ctc agt gcc tct ctg ggc agc aca cag agt tgc cca ctc	3927
Ser Asp Leu Ser Ala Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu	
1230 1235 1240	
cac cct gta ccc atc atg ccc act gca ggc aca act cca gat gaa	3972
His Pro Val Pro Ile Met Pro Thr Ala Gly Thr Thr Pro Asp Glu	
1245 1250 1255	
gac tat gaa tat atg aat cgg caa cga gat gga ggt ggt cct ggg	4017
Asp Tyr Glu Tyr Met Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly	
1260 1265 1270	
ggg gat tat gca gcc atg ggg gcc tgc cca gca tct gag caa ggg	4062
Gly Asp Tyr Ala Ala Met Gly Ala Cys Pro Ala Ser Glu Gln Gly	
1275 1280 1285	
tat gaa gag atg aga gct ttt cag ggg cct gga cat cag gcc ccc	4107
Tyr Glu Glu Met Arg Ala Phe Gln Gly Pro Gly His Gln Ala Pro	
1290 1295 1300	
cat gtc cat tat gcc cgc cta aaa act cta cgt agc tta gag gct	4152
His Val His Tyr Ala Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala	
1305 1310 1315	
aca gac tct gcc ttt gat aac cct gat tac tgg cat agc agg ctt	4197
Thr Asp Ser Ala Phe Asp Asn Pro Asp Tyr Trp His Ser Arg Leu	
1320 1325 1330	
ttc ccc aag gct aat gcc cag aga acg taa ctctgtctcc ctgtggcact	4247
Phe Pro Lys Ala Asn Ala Gln Arg Thr	
1335 1340	
cagggagcat ttaatggcag ctagtgcctt tagagggtac cgtcttctcc ctattccctc	4307
tctctcccag gtcccagccc cttttcccca gtcccagaca attccattca atctttggag	4367
gcttttaaac attttgacac aaaattctta tggatatgtag ccagctgtgc actttcttct	4427
ctttcccaac cccaggaaag gttttcctta ttttgtgtgc tttcccagtc ccattcctca	4487
gcttcttcac aggcactcct ggagatatga aggattactc tccatatccc ttctctcag	4547



## 49321-137.ST25.txt

gctcttgact acttgggaact aggctcttat gtgtgccttt gtttcccatc agactgtcaa 4607  
gaagaggaaa gggaggaaac ctagcagagg aaagtgtaat tttggtttat gactcttaac 4667  
cccctagaaa gacagaagct taaaatctgt gaagaaagag gttaggagta gatattgatt 4727  
actatcataa ttcagcactt aactatgagc caggcatcat actaaacttc acctacatta 4787  
tctcaacttag tcctttatca tccttaaaac aattctgtga catacatatt atctcatttt 4847  
acacaaaggg aagtcgggca tgggtggctca tgcctgtaat ctcagcactt tgggaggctg 4907  
aggcagaagg attacctgag gcaaggagtt tgagaccagc ttagccaaca tagtaagacc 4967  
cccatctc 4975

<210> 14  
<211> 1342  
<212> PRT  
<213> Homo sapiens

<400> 14

Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly Leu Leu Phe Ser Leu  
1 5 10 15

Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala Val Cys Pro Gly Thr  
20 25 30

Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu Asn Gln Tyr Gln Thr  
35 40 45

Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val Met Gly Asn Leu Glu  
50 55 60

Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile  
65 70 75 80

Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Thr  
85 90 95

Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp  
100 105 110

Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser  
115 120 125

His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu Thr Glu Ile Leu Ser  
130 135 140

## 49321-137.ST25.txt

Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr  
 145 150 155 160  
 Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp Ala Glu Ile Val Val  
 165 170 175  
 Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His Glu Val Cys Lys Gly  
 180 185 190  
 Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln Thr Leu Thr Lys Thr  
 195 200 205  
 Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe Gly Pro Asn Pro Asn  
 210 215 220  
 Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp  
 225 230 235 240  
 Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp Ser Gly Ala Cys Val  
 245 250 255  
 Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu  
 260 265 270  
 Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala  
 275 280 285  
 Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Ser Cys Val Arg Ala  
 290 295 300  
 Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys  
 305 310 315 320  
 Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys Glu Gly Thr Gly Ser  
 325 330 335  
 Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn Ile Asp Gly Phe Val  
 340 345 350  
 Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gly Leu  
 355 360 365  
 Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu Asp Pro Glu Lys Leu  
 370 375 380

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Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly Tyr Leu Asn Ile Gln  
385 390 395 400

Ser Trp Pro Pro His Met His Asn Phe Ser Val Phe Ser Asn Leu Thr  
405 410 415

Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu Ile  
420 425 430

Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe Arg Ser Leu Lys Glu  
435 440 445

Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn Arg Gln Leu Cys Tyr  
450 455 460

His His Ser Leu Asn Trp Thr Lys Val Leu Arg Gly Pro Thr Glu Glu  
465 470 475 480

Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg Asp Cys Val Ala Glu  
485 490 495

Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly Pro  
500 505 510

Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr Ser Arg Gly Gly Val  
515 520 525

Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu Pro Arg Glu Phe Ala  
530 535 540

His Glu Ala Glu Cys Phe Ser Cys His Pro Glu Cys Gln Pro Met Glu  
545 550 555 560

Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp Thr Cys Ala Gln Cys  
565 570 575

Ala His Phe Arg Asp Gly Pro His Cys Val Ser Ser Cys Pro His Gly  
580 585 590

Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr Pro Asp Val Gln Asn  
595 600 605

Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln Gly Cys Lys Gly Pro

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610

615

620

Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val Leu Ile Gly Lys Thr  
 625 630 635 640

His Leu Thr Met Ala Leu Thr Val Ile Ala Gly Leu Val Val Ile Phe  
 645 650 655

Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile Gln  
 660 665 670

Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg Gly Glu Ser Ile Glu  
 675 680 685

Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val Leu Ala Arg Ile Phe  
 690 695 700

Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Val Phe  
 705 710 715 720

Gly Thr Val His Lys Gly Val Trp Ile Pro Glu Gly Glu Ser Ile Lys  
 725 730 735

Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys Ser Gly Arg Gln Ser  
 740 745 750

Phe Gln Ala Val Thr Asp His Met Leu Ala Ile Gly Ser Leu Asp His  
 755 760 765

Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro Gly Ser Ser Leu Gln  
 770 775 780

Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu Leu Asp His Val Arg  
 785 790 795 800

Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu Leu Asn Trp Gly Val  
 805 810 815

Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu His Gly Met Val His  
 820 825 830

Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys Ser Pro Ser Gln Val  
 835 840 845

## 49321-137.ST25.txt

Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu Pro Pro Asp Asp Lys  
 850 855 860

Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile Lys Trp Met Ala Leu  
 865 870 875 880

Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln Ser Asp Val Trp Ser  
 885 890 895

Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala Glu Pro Tyr  
 900 905 910

Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu Leu Glu Lys Gly Glu  
 915 920 925

Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr Met Val Met  
 930 935 940

Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg Pro Thr Phe Lys Glu  
 945 950 955 960

Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp Pro Pro Arg Tyr Leu  
 965 970 975

Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu Pro  
 980 985 990

His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val Glu Leu Glu Pro Glu  
 995 1000 1005

Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu Glu Asp Asn Leu Ala  
 1010 1015 1020

Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu Pro Val Gly Thr Leu  
 1025 1030 1035

Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu Ser Pro Ser Ser Gly  
 1040 1045 1050

Tyr Met Pro Met Asn Gln Gly Asn Leu Gly Gly Ser Cys Gln Glu  
 1055 1060 1065

Ser Ala Val Ser Gly Ser Ser Glu Arg Cys Pro Arg Pro Val Ser  
 1070 1075 1080

## 49321-137.ST25.txt

Leu His Pro Met Pro Arg Gly Cys Leu Ala Ser Glu Ser Ser Glu  
 1085 1090 1095  
  
 Gly His Val Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser  
 1100 1105 1110  
  
 Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly  
 1115 1120 1125  
  
 Asp Ser Ala Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val  
 1130 1135 1140  
  
 Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu Glu Asp Val Asn Gly  
 1145 1150 1155  
  
 Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg  
 1160 1165 1170  
  
 Glu Gly Thr Leu Ser Ser Val Gly Leu Ser Ser Val Leu Gly Thr  
 1175 1180 1185  
  
 Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Arg  
 1190 1195 1200  
  
 Arg Arg His Ser Pro Pro His Pro Pro Arg Pro Ser Ser Leu Glu  
 1205 1210 1215  
  
 Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu Ser Ala  
 1220 1225 1230  
  
 Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile  
 1235 1240 1245  
  
 Met Pro Thr Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu Tyr Met  
 1250 1255 1260  
  
 Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly Gly Asp Tyr Ala Ala  
 1265 1270 1275  
  
 Met Gly Ala Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu Met Arg  
 1280 1285 1290  
  
 Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala  
 1295 1300 1305

## 49321-137.ST25.txt

Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala Thr Asp Ser Ala Phe  
 1310 1315 1320

Asp Asn Pro Asp Tyr Trp His Ser Arg Leu Phe Pro Lys Ala Asn  
 1325 1330 1335

Ala Gln Arg Thr  
 1340

<210> 15  
 <211> 5484  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (34)..(3960)  
 <223> HER-4 coding sequence

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 Met Lys Pro Ala Thr Gly Leu  
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tgg gtc tgg gtg agc ctt ctc gtg gcg gcg ggg acc gtc cag ccc agc 102  
 Trp Val Trp Val Ser Leu Leu Val Ala Ala Gly Thr Val Gln Pro Ser  
 10 15 20

gat tct cag tca gtg tgt gca gga acg gag aat aaa ctg agc tct ctc 150  
 Asp Ser Gln Ser Val Cys Ala Gly Thr Glu Asn Lys Leu Ser Ser Leu  
 25 30 35

tct gac ctg gaa cag cag tac cga gcc ttg cgc aag tac tat gaa aac 198  
 Ser Asp Leu Glu Gln Gln Tyr Arg Ala Leu Arg Lys Tyr Tyr Glu Asn  
 40 45 50 55

tgt gag gtt gtc atg ggc aac ctg gag ata acc agc att gag cac aac 246  
 Cys Glu Val Val Met Gly Asn Leu Glu Ile Thr Ser Ile Glu His Asn  
 60 65 70

cgg gac ctc tcc ttc ctg cgg tct gtt cga gaa gtc aca ggc tac gtg 294  
 Arg Asp Leu Ser Phe Leu Arg Ser Val Arg Glu Val Thr Gly Tyr Val  
 75 80 85

tta gtg gct ctt aat cag ttt cgt tac ctg cct ctg gag aat tta cgc 342  
 Leu Val Ala Leu Asn Gln Phe Arg Tyr Leu Pro Leu Glu Asn Leu Arg  
 90 95 100

att att cgt ggg aca aaa ctt tat gag gat cga tat gcc ttg gca ata 390  
 Ile Ile Arg Gly Thr Lys Leu Tyr Glu Asp Arg Tyr Ala Leu Ala Ile  
 105 110 115

ttt tta aac tac aga aaa gat gga aac ttt gga ctt caa gaa ctt gga 438

## 49321-137.ST25.txt

Phe 120	Leu	Asn	Tyr	Arg	Lys 125	Asp	Gly	Asn	Phe	Gly 130	Leu	Gln	Glu	Leu	Gly 135	
tta	aag	aac	ttg	aca	gaa	atc	cta	aat	ggg	gga	gtc	tat	gta	gac	cag	486
Leu	Lys	Asn	Leu	Thr 140	Glu	Ile	Leu	Asn	Gly 145	Gly	Val	Tyr	Val	Asp 150	Gln	
aac	aaa	ttc	ctt	tgt	tat	gca	gac	acc	att	cat	tgg	caa	gat	att	gtt	534
Asn	Lys	Phe	Leu	Cys 155	Tyr	Ala	Asp	Thr 160	Ile	His	Trp	Gln	Asp 165	Ile	Val	
cgg	aac	cca	tgg	cct	tcc	aac	ttg	act	ctt	gtg	tca	aca	aat	ggg	agt	582
Arg	Asn	Pro	Trp	Pro	Ser	Asn	Leu 175	Thr	Leu	Val	Ser	Thr 180	Asn	Gly	Ser	
tca	gga	tgt	gga	cgt	tgc	cat	aag	tcc	tgt	act	ggc	cgt	tgc	tgg	gga	630
Ser	Gly	Cys	Gly	Arg	Cys	His 190	Lys	Ser	Cys	Thr	Gly 195	Arg	Cys	Trp	Gly	
ccc	aca	gaa	aat	cat	tgc	cag	act	ttg	aca	agg	acg	gtg	tgt	gca	gaa	678
Pro	Thr	Glu	Asn	His	Cys	Gln 205	Thr	Leu	Thr	Arg 210	Thr	Val	Cys	Ala	Glu 215	
caa	tgt	gac	ggc	aga	tgc	tac	gga	cct	tac	gtc	agt	gac	tgc	tgc	cat	726
Gln	Cys	Asp	Gly	Arg	Cys	Tyr 220	Gly	Pro	Tyr 225	Val	Ser	Asp	Cys	Cys	His 230	
cga	gaa	tgt	gct	gga	ggc	tgc	tca	gga	cct	aag	gac	aca	gac	tgc	ttt	774
Arg	Glu	Cys	Ala	Gly	Gly	Cys 235	Ser	Gly 240	Pro	Lys	Asp	Thr 245	Asp	Cys	Phe	
gcc	tgc	atg	aat	ttc	aat	gac	agt	gga	gca	tgt	gtt	act	cag	tgt	ccc	822
Ala	Cys	Met	Asn	Phe	Asn	Asp 255	Ser	Gly	Ala	Cys	Val	Thr 260	Gln	Cys	Pro	
caa	acc	ttt	gtc	tac	aat	cca	acc	acc	ttt	caa	ctg	gag	cac	aat	ttc	870
Gln	Thr	Phe	Val	Tyr	Asn	Pro 270	Thr	Thr	Phe	Gln	Leu 275	Glu	His	Asn	Phe	
aat	gca	aag	tac	aca	tat	gga	gca	ttc	tgt	gtc	aag	aaa	tgt	cca	cat	918
Asn	Ala	Lys	Tyr	Thr	Tyr	Gly 285	Ala	Phe	Cys	Val 290	Lys	Lys	Cys	Pro	His 295	
aac	ttt	gtg	gta	gat	tcc	agt	tct	tgt	gtg	cgt	gcc	tgc	cct	agt	tcc	966
Asn	Phe	Val	Val	Asp 300	Ser	Ser	Ser	Cys	Val 305	Arg	Ala	Cys	Pro	Ser 310	Ser	
aag	atg	gaa	gta	gaa	gaa	aat	ggg	att	aaa	atg	tgt	aaa	cct	tgc	act	1014
Lys	Met	Glu	Val	Glu	Glu	Asn 315	Gly	Ile 320	Lys	Met	Cys	Lys	Pro 325	Cys	Thr	
gac	att	tgc	cca	aaa	gct	tgt	gat	ggc	att	ggc	aca	gga	tca	ttg	atg	1062
Asp	Ile	Cys	Pro	Lys	Ala	Cys 330	Asp	Gly 335	Ile	Gly	Thr 340	Gly	Ser	Leu	Met	
tca	gct	cag	act	gtg	gat	tcc	agt	aac	att	gac	aaa	ttc	ata	aac	tgt	1110
Ser	Ala	Gln	Thr	Val	Asp 345	Ser	Ser	Asn 350	Ile	Asp	Lys 355	Phe	Ile	Asn	Cys	



## 49321-137.ST25.txt

acc aag atc aat ggg aat ttg atc ttt cta gtc act ggt att cat ggg	1158
Thr Lys Ile Asn Gly Asn Leu Ile Phe Leu Val Thr Gly Ile His Gly	
360 365 370 375	
gac cct tac aat gca att gaa gcc ata gac cca gag aaa ctg aac gtc	1206
Asp Pro Tyr Asn Ala Ile Glu Ala Ile Asp Pro Glu Lys Leu Asn Val	
380 385 390	
ttt cgg aca gtc aga gag ata aca ggt' ttc ctg aac ata cag tca tgg	1254
Phe Arg Thr Val Arg Glu Ile Thr Gly Phe Leu Asn Ile Gln Ser Trp	
395 400 405	
cca cca aac atg act gac ttc agt gtt ttt tct aac ctg gtg acc att	1302
Pro Pro Asn Met Thr Asp Phe Ser Val Phe Ser Asn Leu Val Thr Ile	
410 415 420	
ggt gga aga gta ctc tat agt ggc ctg tcc ttg ctt atc ctc aag caa	1350
Gly Gly Arg Val Leu Tyr Ser Gly Leu Ser Leu Leu Ile Leu Lys Gln	
425 430 435	
cag ggc atc acc tct cta cag ttc cag tcc ctg aag gaa atc agc gca	1398
Gln Gly Ile Thr Ser Leu Gln Phe Gln Ser Leu Lys Glu Ile Ser Ala	
440 445 450 455	
gga aac atc tat att act gac aac agc aac ctg tgt tat tat cat acc	1446
Gly Asn Ile Tyr Ile Thr Asp Asn Ser Asn Leu Cys Tyr Tyr His Thr	
460 465 470	
att aac tgg aca aca ctc ttc agc aca atc aac cag aga ata gta atc	1494
Ile Asn Trp Thr Thr Leu Phe Ser Thr Ile Asn Gln Arg Ile Val Ile	
475 480 485	
cgg gac aac aga aaa gct gaa aat tgt act gct gaa gga atg gtg tgc	1542
Arg Asp Asn Arg Lys Ala Glu Asn Cys Thr Ala Glu Gly Met Val Cys	
490 495 500	
aac cat ctg tgt tcc agt gat ggc tgt tgg gga cct ggg cca gac caa	1590
Asn His Leu Cys Ser Ser Asp Gly Cys Trp Gly Pro Gly Pro Asp Gln	
505 510 515	
tgt ctg tcg tgt cgc cgc ttc agt aga gga agg atc tgc ata gag tct	1638
Cys Leu Ser Cys Arg Arg Phe Ser Arg Gly Arg Ile Cys Ile Glu Ser	
520 525 530 535	
tgt aac ctc tat gat ggt gaa ttt cgg gag ttt gag aat ggc tcc atc	1686
Cys Asn Leu Tyr Asp Gly Glu Phe Arg Glu Phe Glu Asn Gly Ser Ile	
540 545 550	
tgt gtg gag tgt gac ccc cag tgt gag aag atg gaa gat ggc ctc ctc	1734
Cys Val Glu Cys Asp Pro Gln Cys Glu Lys Met Glu Asp Gly Leu Leu	
555 560 565	
aca tgc cat gga ccg ggt cct gac aac tgt aca aag tgc tct cat ttt	1782
Thr Cys His Gly Pro Gly Pro Asp Asn Cys Thr Lys Cys Ser His Phe	
570 575 580	
aaa gat ggc cca aac tgt gtg gaa aaa tgt cca gat ggc tta cag ggg	1830
Lys Asp Gly Pro Asn Cys Val Glu Lys Cys Pro Asp Gly Leu Gln Gly	
585 590 595	

## 49321-137.ST25.txt

gca aac agt ttc att ttc aag tat gct gat cca gat cgg gag tgc cac	1878
Ala Asn Ser Phe Ile Phe Lys Tyr Ala Asp Pro Asp Arg Glu Cys His	
600 605 610 615	
cca tgc cat cca aac tgc acc caa ggg tgt aac ggt ccc act agt cat	1926
Pro Cys His Pro Asn Cys Thr Gln Gly Cys Asn Gly Pro Thr Ser His	
620 625 630	
gac tgc att tac tac cca tgg acg ggc cat tcc act tta cca caa cat	1974
Asp Cys Ile Tyr Tyr Pro Trp Thr Gly His Ser Thr Leu Pro Gln His	
635 640 645	
gct aga act ccc ctg att gca gct gga gta att ggt ggg ctc ttc att	2022
Ala Arg Thr Pro Leu Ile Ala Ala Gly Val Ile Gly Gly Leu Phe Ile	
650 655 660	
ctg gtc att gtg ggt ctg aca ttt gct gtt tat gtt aga agg aag agc	2070
Leu Val Ile Val Gly Leu Thr Phe Ala Val Tyr Val Arg Arg Lys Ser	
665 670 675	
atc aaa aag aaa aga gcc ttg aga aga ttc ttg gaa aca gag ttg gtg	2118
Ile Lys Lys Lys Arg Ala Leu Arg Arg Phe Leu Glu Thr Glu Leu Val	
680 685 690 695	
gaa cca tta act ccc agt ggc aca gca ccc aat caa gct caa ctt cgt	2166
Glu Pro Leu Thr Pro Ser Gly Thr Ala Pro Asn Gln Ala Gln Leu Arg	
700 705 710	
att ttg aaa gaa act gag ctg aag agg gta aaa gtc ctt ggc tca ggt	2214
Ile Leu Lys Glu Thr Glu Leu Lys Arg Val Lys Val Leu Gly Ser Gly	
715 720 725	
gct ttt gga acg gtt tat aaa ggt att tgg gta cct gaa gga gaa act	2262
Ala Phe Gly Thr Val Tyr Lys Gly Ile Trp Val Pro Glu Gly Glu Thr	
730 735 740	
gtg aag att cct gtg gct att aag att ctt aat gag aca act ggt ccc	2310
Val Lys Ile Pro Val Ala Ile Lys Ile Leu Asn Glu Thr Thr Gly Pro	
745 750 755	
aag gca aat gtg gag ttc atg gat gaa gct ctg atc atg gca agt atg	2358
Lys Ala Asn Val Glu Phe Met Asp Glu Ala Leu Ile Met Ala Ser Met	
760 765 770 775	
gat cat cca cac cta gtc cgg ttg ctg ggt gtg tgt ctg agc cca acc	2406
Asp His Pro His Leu Val Arg Leu Leu Gly Val Cys Leu Ser Pro Thr	
780 785 790	
atc cag ctg gtt act caa ctt atg ccc cat ggc tgc ctg ttg gag tat	2454
Ile Gln Leu Val Thr Gln Leu Met Pro His Gly Cys Leu Leu Glu Tyr	
795 800 805	
gtc cac gag cac aag gat aac att gga tca caa ctg ctg ctt aac tgg	2502
Val His Glu His Lys Asp Asn Ile Gly Ser Gln Leu Leu Leu Asn Trp	
810 815 820	
tgt gtc cag ata gct aag gga atg atg tac ctg gaa gaa aga cga ctc	2550
Cys Val Gln Ile Ala Lys Gly Met Met Tyr Leu Glu Glu Arg Arg Leu	

## 49321-137.ST25.txt

825	830	835	
gtt cat cgg gat ttg gca gcc cgt aat gtc tta gtg aaa tct cca aac Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Ser Pro Asn 840 845 850 855			2598
cat gtg aaa atc aca gat ttt ggg cta gcc aga ctc ttg gaa gga gat His Val Lys Ile Thr Asp Phe Gly Leu Ala Arg Leu Leu Glu Gly Asp 860 865 870			2646
gaa aaa gag tac aat gct gat gga gga aag atg cca att aaa tgg atg Glu Lys Glu Tyr Asn Ala Asp Gly Gly Lys Met Pro Ile Lys Trp Met 875 880 885			2694
gct ctg gag tgt ata cat tac agg aaa ttc acc cat cag agt gac gtt Ala Leu Glu Cys Ile His Tyr Arg Lys Phe Thr His Gln Ser Asp Val 890 895 900			2742
tgg agc tat gga gtt act ata tgg gaa ctg atg acc ttt gga gga aaa Trp Ser Tyr Gly Val Thr Ile Trp Glu Leu Met Thr Phe Gly Gly Lys 905 910 915			2790
ccc tat gat gga att cca acg cga gaa atc cct gat tta tta gag aaa Pro Tyr Asp Gly Ile Pro Thr Arg Glu Ile Pro Asp Leu Leu Glu Lys 920 925 930 935			2838
gga gaa cgt ttg cct cag cct ccc atc tgc act att gac gtt tac atg Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr Met 940 945 950			2886
gtc atg gtc aaa tgt tgg atg att gat gct gac agt aga cct aaa ttt Val Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys Phe 955 960 965			2934
aag gaa ctg gct gct gag ttt tca agg atg gct cga gac cct caa aga Lys Glu Leu Ala Ala Glu Phe Ser Arg Met Ala Arg Asp Pro Gln Arg 970 975 980			2982
tac cta gtt att cag ggt gat gat cgt atg aag ctt ccc agt cca aat Tyr Leu Val Ile Gln Gly Asp Asp Arg Met Lys Leu Pro Ser Pro Asn 985 990 995			3030
gac agc aag ttc ttt cag aat ctc ttg gat gaa gag gat ttg gaa Asp Ser Lys Phe Phe Gln Asn Leu Leu Asp Glu Glu Asp Leu Glu 1000 1005 1010			3075
gat atg atg gat gct gag gag tac ttg gtc cct cag gct ttc aac Asp Met Met Asp Ala Glu Glu Tyr Leu Val Pro Gln Ala Phe Asn 1015 1020 1025			3120
atc cca cct ccc atc tat act tcc aga gca aga att gac tcg aat Ile Pro Pro Pro Ile Tyr Thr Ser Arg Ala Arg Ile Asp Ser Asn 1030 1035 1040			3165
agg agt gaa att gga cac agc cct cct cct gcc tac acc ccc atg Arg Ser Glu Ile Gly His Ser Pro Pro Pro Ala Tyr Thr Pro Met 1045 1050 1055			3210
tca gga aac cag ttt gta tac cga gat gga ggt ttt gct gct gaa			3255

## 49321-137.ST25.txt

Ser 1060	Gly	Asn	Gln	Phe	Val 1065	Tyr	Arg	Asp	Gly	Gly 1070	Phe	Ala	Ala	Glu	
caa	gga	gtg	tct	gtg	ccc	tac	aga	gcc	cca	act	agc	aca	att	cca	3300
Gln 1075	Gly	Val	Ser	Val	Pro 1080	Tyr	Arg	Ala	Pro	Thr 1085	Ser	Thr	Ile	Pro	
gaa	gct	cct	gtg	gca	cag	ggc	gct	act	gct	gag	att	ttt	gat	gac	3345
Glu 1090	Ala	Pro	Val	Ala	Gln 1095	Gly	Ala	Thr	Ala	Glu 1100	Ile	Phe	Asp	Asp	
tcc	tgc	tgt	aat	ggc	acc	cta	cgc	aag	cca	gtg	gca	ccc	cat	gtc	3390
Ser 1105	Cys	Cys	Asn	Gly	Thr 1110	Leu	Arg	Lys	Pro	Val 1115	Ala	Pro	His	Val	
caa	gag	gac	agt	agc	acc	cag	agg	tac	agt	gct	gac	ccc	acc	gtg	3435
Gln 1120	Glu	Asp	Ser	Ser	Thr 1125	Gln	Arg	Tyr	Ser	Ala 1130	Asp	Pro	Thr	Val	
ttt	gcc	cca	gaa	cgg	agc	cca	cga	gga	gag	ctg	gat	gag	gaa	ggc	3480
Phe 1135	Ala	Pro	Glu	Arg	Ser 1140	Pro	Arg	Gly	Glu	Leu 1145	Asp	Glu	Glu	Gly	
tac	atg	act	cct	atg	cga	gac	aaa	ccc	aaa	caa	gaa	tac	ctg	aat	3525
Tyr 1150	Met	Thr	Pro	Met	Arg 1155	Asp	Lys	Pro	Lys	Gln 1160	Glu	Tyr	Leu	Asn	
cca	gtg	gag	gag	aac	cct	ttt	gtt	tct	cgg	aga	aaa	aat	gga	gac	3570
Pro 1165	Val	Glu	Glu	Asn	Pro 1170	Phe	Val	Ser	Arg	Arg 1175	Lys	Asn	Gly	Asp	
ctt	caa	gca	ttg	gat	aat	ccc	gaa	tat	cac	aat	gca	tcc	aat	ggc	3615
Leu 1180	Gln	Ala	Leu	Asp	Asn 1185	Pro	Glu	Tyr	His	Asn 1190	Ala	Ser	Asn	Gly	
cca	ccc	aag	gcc	gag	gat	gag	tat	gtg	aat	gag	cca	ctg	tac	ctc	3660
Pro 1195	Pro	Lys	Ala	Glu	Asp 1200	Glu	Tyr	Val	Asn	Glu 1205	Pro	Leu	Tyr	Leu	
aac	acc	ttt	gcc	aac	acc	ttg	gga	aaa	gct	gag	tac	ctg	aag	aac	3705
Asn 1210	Thr	Phe	Ala	Asn	Thr 1215	Leu	Gly	Lys	Ala	Glu 1220	Tyr	Leu	Lys	Asn	
aac	ata	ctg	tca	atg	cca	gag	aag	gcc	aag	aaa	gcg	ttt	gac	aac	3750
Asn 1225	Ile	Leu	Ser	Met	Pro 1230	Glu	Lys	Ala	Lys	Lys 1235	Ala	Phe	Asp	Asn	
cct	gac	tac	tgg	aac	cac	agc	ctg	cca	cct	cgg	agc	acc	ctt	cag	3795
Pro 1240	Asp	Tyr	Trp	Asn	His 1245	Ser	Leu	Pro	Pro	Arg 1250	Ser	Thr	Leu	Gln	
cac	cca	gac	tac	ctg	cag	gag	tac	agc	aca	aaa	tat	ttt	tat	aaa	3840
His 1255	Pro	Asp	Tyr	Leu	Gln 1260	Glu	Tyr	Ser	Thr	Lys 1265	Tyr	Phe	Tyr	Lys	
cag	aat	ggg	cgg	atc	cgg	cct	att	gtg	gca	gag	aat	cct	gaa	tac	3885
Gln 1270	Asn	Gly	Arg	Ile	Arg 1275	Pro	Ile	Val	Ala	Glu 1280	Asn	Pro	Glu	Tyr	

## 49321-137.ST25.txt

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ctc tct gag ttc tcc ctg aag cca ggc act gtg ctg ccg cct cca 3930
Leu Ser Glu Phe Ser Leu Lys Pro Gly Thr Val Leu Pro Pro Pro
1285 1290 1295

cct tac aga cac cgg aat act gtg gtg taa gctcagttgt gggttttttag 3980
Pro Tyr Arg His Arg Asn Thr Val Val
1300 1305

gtggagagac acacctgctc caatttcccc accccctct ctttctctgg tggctcttct 4040

tctaccccaa ggccagtagt tttgacactt cccagtggaa gatacagaga tgcaatgata 4100

gttatgtgct tacctaactt gaacattaga gggaaagact gaaagagaaa gataggagga 4160

accacaatgt ttcttcattt ctctgcatgg gttggtcagg agaatgaaac agctagagaa 4220

ggaccagaaa atgtaaggca atgctgccta ctatcaaact agctgtcact ttttttcttt 4280

ttctttttct ttctttgttt ctttcttctt cttctttttt tttttttttt taaagcagat 4340

ggttgaaaca cccatgctat ctgttcctat ctgcaggaac tgatgtgtgc atatttagca 4400

tccctggaaa tcataataaa gtttccatta gaacaaaaga ataacatttt ctataacata 4460

tgatagtgtc tgaaattgag aatccagttt ctttccccag cagtttctgt cctagcaagt 4520

aagaatggcc aactcaactt tcataattta aaaatctcca ttaaagttat aactagtaat 4580

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tcacagaatt taagcaagaa atattttaat atagtgaat ggccactact ttaagtatac 4760

aatctttaa aaagaaagg gaggctaata tttttcatgc tatcaaatta tcttcaccct 4820

catcctttac atttttcaac attttttttt ctcataaat gacactactt gataggccgt 4880

tggttgctctg aagagtagaa gggaaactaa gagacagttc tctgtggttc aggaaaacta 4940

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ttgggtatgt ctacctggca gatactcaga aatgtagttt gcacttaagc tgtaatttta 5060

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caaaccaagc aaattaggaa ccttgcaacg gtatccaggg actatgatga gaggccagca 5240

cattatcttc atatgtcacc tttgtacgc aaggaaattt gttcagttcg tatacttcgt 5300

aagaaggaat gcgagtaagg attggcttga attccatgga atttctagta tgagactatt 5360

tatatgaagt agaaggtaac tctttgcaca taaattggta taataaaaag aaaaacacaa 5420

acattcaaag cttagggata ggtccttggg tcaaaagttg taaataaatg tgaaacatct 5480

tctc 5484

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49321-137.ST25.txt

&lt;210&gt; 16

&lt;211&gt; 1308

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

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Ala Gly Thr Val Gln Pro Ser Asp Ser Gln Ser Val Cys Ala Gly Thr  
 20 25 30

Glu Asn Lys Leu Ser Ser Leu Ser Asp Leu Glu Gln Gln Tyr Arg Ala  
 35 40 45

Leu Arg Lys Tyr Tyr Glu Asn Cys Glu Val Val Met Gly Asn Leu Glu  
 50 55 60

Ile Thr Ser Ile Glu His Asn Arg Asp Leu Ser Phe Leu Arg Ser Val  
 65 70 75 80

Arg Glu Val Thr Gly Tyr Val Leu Val Ala Leu Asn Gln Phe Arg Tyr  
 85 90 95

Leu Pro Leu Glu Asn Leu Arg Ile Ile Arg Gly Thr Lys Leu Tyr Glu  
 100 105 110

Asp Arg Tyr Ala Leu Ala Ile Phe Leu Asn Tyr Arg Lys Asp Gly Asn  
 115 120 125

Phe Gly Leu Gln Glu Leu Gly Leu Lys Asn Leu Thr Glu Ile Leu Asn  
 130 135 140

Gly Gly Val Tyr Val Asp Gln Asn Lys Phe Leu Cys Tyr Ala Asp Thr  
 145 150 155 160

Ile His Trp Gln Asp Ile Val Arg Asn Pro Trp Pro Ser Asn Leu Thr  
 165 170 175

Leu Val Ser Thr Asn Gly Ser Ser Gly Cys Gly Arg Cys His Lys Ser  
 180 185 190

Cys Thr Gly Arg Cys Trp Gly Pro Thr Glu Asn His Cys Gln Thr Leu  
 195 200 205

49321-137.ST25.txt

Thr Arg Thr Val Cys Ala Glu Gln Cys Asp Gly Arg Cys Tyr Gly Pro  
 210 215 220

Tyr Val Ser Asp Cys Cys His Arg Glu Cys Ala Gly Gly Cys Ser Gly  
 225 230 235 240

Pro Lys Asp Thr Asp Cys Phe Ala Cys Met Asn Phe Asn Asp Ser Gly  
 245 250 255

Ala Cys Val Thr Gln Cys Pro Gln Thr Phe Val Tyr Asn Pro Thr Thr  
 260 265 270

Phe Gln Leu Glu His Asn Phe Asn Ala Lys Tyr Thr Tyr Gly Ala Phe  
 275 280 285

Cys Val Lys Lys Cys Pro His Asn Phe Val Val Asp Ser Ser Ser Cys  
 290 295 300

Val Arg Ala Cys Pro Ser Ser Lys Met Glu Val Glu Glu Asn Gly Ile  
 305 310 315 320

Lys Met Cys Lys Pro Cys Thr Asp Ile Cys Pro Lys Ala Cys Asp Gly  
 325 330 335

Ile Gly Thr Gly Ser Leu Met Ser Ala Gln Thr Val Asp Ser Ser Asn  
 340 345 350

Ile Asp Lys Phe Ile Asn Cys Thr Lys Ile Asn Gly Asn Leu Ile Phe  
 355 360 365

Leu Val Thr Gly Ile His Gly Asp Pro Tyr Asn Ala Ile Glu Ala Ile  
 370 375 380

Asp Pro Glu Lys Leu Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly  
 385 390 395 400

Phe Leu Asn Ile Gln Ser Trp Pro Pro Asn Met Thr Asp Phe Ser Val  
 405 410 415

Phe Ser Asn Leu Val Thr Ile Gly Gly Arg Val Leu Tyr Ser Gly Leu  
 420 425 430

Ser Leu Leu Ile Leu Lys Gln Gln Gly Ile Thr Ser Leu Gln Phe Gln

49321-137.ST25.txt

435

440

445

Ser Leu Lys Glu Ile Ser Ala Gly Asn Ile Tyr Ile Thr Asp Asn Ser  
 450 455 460

Asn Leu Cys Tyr Tyr His Thr Ile Asn Trp Thr Thr Leu Phe Ser Thr  
 465 470 475 480

Ile Asn Gln Arg Ile Val Ile Arg Asp Asn Arg Lys Ala Glu Asn Cys  
 485 490 495

Thr Ala Glu Gly Met Val Cys Asn His Leu Cys Ser Ser Asp Gly Cys  
 500 505 510

Trp Gly Pro Gly Pro Asp Gln Cys Leu Ser Cys Arg Arg Phe Ser Arg  
 515 520 525

Gly Arg Ile Cys Ile Glu Ser Cys Asn Leu Tyr Asp Gly Glu Phe Arg  
 530 535 540

Glu Phe Glu Asn Gly Ser Ile Cys Val Glu Cys Asp Pro Gln Cys Glu  
 545 550 555 560

Lys Met Glu Asp Gly Leu Leu Thr Cys His Gly Pro Gly Pro Asp Asn  
 565 570 575

Cys Thr Lys Cys Ser His Phe Lys Asp Gly Pro Asn Cys Val Glu Lys  
 580 585 590

Cys Pro Asp Gly Leu Gln Gly Ala Asn Ser Phe Ile Phe Lys Tyr Ala  
 595 600 605

Asp Pro Asp Arg Glu Cys His Pro Cys His Pro Asn Cys Thr Gln Gly  
 610 615 620

Cys Asn Gly Pro Thr Ser His Asp Cys Ile Tyr Tyr Pro Trp Thr Gly  
 625 630 635 640

His Ser Thr Leu Pro Gln His Ala Arg Thr Pro Leu Ile Ala Ala Gly  
 645 650 655

Val Ile Gly Gly Leu Phe Ile Leu Val Ile Val Gly Leu Thr Phe Ala  
 660 665 670



49321-137.ST25.txt

Val Tyr Val Arg Arg Lys Ser Ile Lys Lys Lys Arg Ala Leu Arg Arg  
 675 680 685

Phe Leu Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Thr Ala  
 690 695 700

Pro Asn Gln Ala Gln Leu Arg Ile Leu Lys Glu Thr Glu Leu Lys Arg  
 705 710 715 720

Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly Ile  
 725 730 735

Trp Val Pro Glu Gly Glu Thr Val Lys Ile Pro Val Ala Ile Lys Ile  
 740 745 750

Leu Asn Glu Thr Thr Gly Pro Lys Ala Asn Val Glu Phe Met Asp Glu  
 755 760 765

Ala Leu Ile Met Ala Ser Met Asp His Pro His Leu Val Arg Leu Leu  
 770 775 780

Gly Val Cys Leu Ser Pro Thr Ile Gln Leu Val Thr Gln Leu Met Pro  
 785 790 795 800

His Gly Cys Leu Leu Glu Tyr Val His Glu His Lys Asp Asn Ile Gly  
 805 810 815

Ser Gln Leu Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Met  
 820 825 830

Tyr Leu Glu Glu Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn  
 835 840 845

Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe Gly Leu  
 850 855 860

Ala Arg Leu Leu Glu Gly Asp Glu Lys Glu Tyr Asn Ala Asp Gly Gly  
 865 870 875 880

Lys Met Pro Ile Lys Trp Met Ala Leu Glu Cys Ile His Tyr Arg Lys  
 885 890 895

Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Ile Trp Glu  
 900 905 910

## 49321-137.ST25.txt

Leu Met Thr Phe Gly Gly Lys Pro Tyr Asp Gly Ile Pro Thr Arg Glu  
 915 920 925

Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile  
 930 935 940

Cys Thr Ile Asp Val Tyr Met Val Met Val Lys Cys Trp Met Ile Asp  
 945 950 955 960

Ala Asp Ser Arg Pro Lys Phe Lys Glu Leu Ala Ala Glu Phe Ser Arg  
 965 970 975

Met Ala Arg Asp Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Asp Arg  
 980 985 990

Met Lys Leu Pro Ser Pro Asn Asp Ser Lys Phe Phe Gln Asn Leu Leu  
 995 1000 1005

Asp Glu Glu Asp Leu Glu Asp Met Met Asp Ala Glu Glu Tyr Leu  
 1010 1015 1020

Val Pro Gln Ala Phe Asn Ile Pro Pro Pro Ile Tyr Thr Ser Arg  
 1025 1030 1035

Ala Arg Ile Asp Ser Asn Arg Ser Glu Ile Gly His Ser Pro Pro  
 1040 1045 1050

Pro Ala Tyr Thr Pro Met Ser Gly Asn Gln Phe Val Tyr Arg Asp  
 1055 1060 1065

Gly Gly Phe Ala Ala Glu Gln Gly Val Ser Val Pro Tyr Arg Ala  
 1070 1075 1080

Pro Thr Ser Thr Ile Pro Glu Ala Pro Val Ala Gln Gly Ala Thr  
 1085 1090 1095

Ala Glu Ile Phe Asp Asp Ser Cys Cys Asn Gly Thr Leu Arg Lys  
 1100 1105 1110

Pro Val Ala Pro His Val Gln Glu Asp Ser Ser Thr Gln Arg Tyr  
 1115 1120 1125

Ser Ala Asp Pro Thr Val Phe Ala Pro Glu Arg Ser Pro Arg Gly  
 1130 1135 1140

## 49321-137.ST25.txt

Glu Leu Asp Glu Glu Gly Tyr Met Thr Pro Met Arg Asp Lys Pro  
 1145 1150 1155

Lys Gln Glu Tyr Leu Asn Pro Val Glu Glu Asn Pro Phe Val Ser  
 1160 1165 1170

Arg Arg Lys Asn Gly Asp Leu Gln Ala Leu Asp Asn Pro Glu Tyr  
 1175 1180 1185

His Asn Ala Ser Asn Gly Pro Pro Lys Ala Glu Asp Glu Tyr Val  
 1190 1195 1200

Asn Glu Pro Leu Tyr Leu Asn Thr Phe Ala Asn Thr Leu Gly Lys  
 1205 1210 1215

Ala Glu Tyr Leu Lys Asn Asn Ile Leu Ser Met Pro Glu Lys Ala  
 1220 1225 1230

Lys Lys Ala Phe Asp Asn Pro Asp Tyr Trp Asn His Ser Leu Pro  
 1235 1240 1245

Pro Arg Ser Thr Leu Gln His Pro Asp Tyr Leu Gln Glu Tyr Ser  
 1250 1255 1260

Thr Lys Tyr Phe Tyr Lys Gln Asn Gly Arg Ile Arg Pro Ile Val  
 1265 1270 1275

Ala Glu Asn Pro Glu Tyr Leu Ser Glu Phe Ser Leu Lys Pro Gly  
 1280 1285 1290

Thr Val Leu Pro Pro Pro Pro Tyr Arg His Arg Asn Thr Val Val  
 1295 1300 1305

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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (46)..(4149)  
 <223> IGF-1R coding sequence

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57

49321-137.ST25.txt

Met Lys Ser Gly

1

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Ser Gly Gly Gly Ser Pro Thr Ser Leu Trp Gly Leu Leu Phe Leu Ser	
5 10 15 20	
gcc gcg ctc tcg ctc tgg ccg acg agt gga gaa atc tgc ggg cca ggc	153
Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile Cys Gly Pro Gly	
25 30 35	
atc gac atc cgc aac gac tat cag cag ctg aag cgc ctg gag aac tgc	201
Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg Leu Glu Asn Cys	
40 45 50	
acg gtg atc gag ggc tac ctc cac atc ctg ctc atc tcc aag gcc gag	249
Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile Ser Lys Ala Glu	
55 60 65	
gac tac cgc agc tac cgc ttc ccc aag ctc acg gtc att acc gag tac	297
Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val Ile Thr Glu Tyr	
70 75 80	
ttg ctg ctg ttc cga gtg gct ggc ctc gag agc ctc gga gac ctc ttc	345
Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu Gly Asp Leu Phe	
85 90 95 100	
ccc aac ctc acg gtc atc cgc ggc tgg aaa ctc ttc tac aac tac gcc	393
Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe Tyr Asn Tyr Ala	
105 110 115	
ctg gtc atc ttc gag atg acc aat ctc aag gat att ggg ctt tac aac	441
Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile Gly Leu Tyr Asn	
120 125 130	
ctg agg aac att act cgg ggg gcc atc agg att gag aaa aat gct gac	489
Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu Lys Asn Ala Asp	
135 140 145	
ctc tgt tac ctc tcc act gtg gac tgg tcc ctg atc ctg gat gcg gtg	537
Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile Leu Asp Ala Val	
150 155 160	
tcc aat aac tac att gtg ggg aat aag ccc cca aag gaa tgt ggg gac	585
Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys Glu Cys Gly Asp	
165 170 175 180	
ctg tgt cca ggg acc atg gag gag aag ccg atg tgt gag aag acc acc	633
Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys Glu Lys Thr Thr	
185 190 195	
atc aac aat gag tac aac tac cgc tgc tgg acc aca aac cgc tgc cag	681
Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr Asn Arg Cys Gln	
200 205 210	
aaa atg tgc cca agc acg tgt ggg aag cgg gcg tgc acc gag aac aat	729
Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys Thr Glu Asn Asn	
215 220 225	

## 49321-137.ST25.txt

gag tgc tgc cac ccc gag tgc ctg ggc agc tgc agc gcg cct gac aac	777
Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser Ala Pro Asp Asn	
230 235 240	
gac acg gcc tgt gta gct tgc cgc cac tac tac tat gcc ggt gtc tgt	825
Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr Ala Gly Val Cys	
245 250 255 260	
gtg cct gcc tgc ccg ccc aac acc tac agg ttt gag ggc tgg cgc tgt	873
Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu Gly Trp Arg Cys	
265 270 275	
gtg gac cgt gac ttc tgc gcc aac atc ctc agc gcc gag agc agc gac	921
Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala Glu Ser Ser Asp	
280 285 290	
tcc gag ggg ttt gtg atc cac gac ggc gag tgc atg cag gag tgc ccc	969
Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met Gln Glu Cys Pro	
295 300 305	
tcg ggc ttc atc cgc aac ggc agc cag agc atg tac tgc atc cct tgt	1017
Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr Cys Ile Pro Cys	
310 315 320	
gaa ggt cct tgc ccg aag gtc tgt gag gaa gaa aag aaa aca aag acc	1065
Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys Lys Thr Lys Thr	
325 330 335 340	
att gat tct gtt act tct gct cag atg ctc caa gga tgc acc atc ttc	1113
Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly Cys Thr Ile Phe	
345 350 355	
aag ggc aat ttg ctc att aac atc cga cgg ggg aat aac att gct tca	1161
Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn Asn Ile Ala Ser	
360 365 370	
gag ctg gag aac ttc atg ggg ctc atc gag gtg gtg acg ggc tac gtg	1209
Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val Thr Gly Tyr Val	
375 380 385	
aag atc cgc cat tct cat gcc ttg gtc tcc ttg tcc ttc cta aaa aac	1257
Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser Phe Leu Lys Asn	
390 395 400	
ctt cgc ctc atc cta gga gag gag cag cta gaa ggg aat tac tcc ttc	1305
Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly Asn Tyr Ser Phe	
405 410 415 420	
tac gtc ctc gac aac cag aac ttg cag caa ctg tgg gac tgg gac cac	1353
Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp Asp Trp Asp His	
425 430 435	
cgc aac ctg acc atc aaa gca ggg aaa atg tac ttt gct ttc aat ccc	1401
Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe Ala Phe Asn Pro	
440 445 450	
aaa tta tgt gtt tcc gaa att tac cgc atg gag gaa gtg acg ggg act	1449
Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu Val Thr Gly Thr	
455 460 465	

## 49321-137.ST25.txt

aaa ggg cgc caa agc aaa ggg gac ata aac acc agg aac aac ggg gag Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg Asn Asn Gly Glu 470 475 480	1497
aga gcc tcc tgt gaa agt gac gtc ctg cat ttc acc tcc acc acc acg Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr Ser Thr Thr Thr 485 490 495 500	1545
tcg aag aat cgc atc atc ata acc tgg cac cgg tac cgg ccc cct gac Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr Arg Pro Pro Asp 505 510 515	1593
tac agg gat ctc atc agc ttc acc gtt tac tac aag gaa gca ccc ttt Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys Glu Ala Pro Phe 520 525 530	1641
aag aat gtc aca gag tat gat ggg cag gat gcc tgc ggc tcc aac agc Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser 535 540 545	1689
tgg aac atg gtg gac gtg gac ctc ccg ccc aac aag gac gtg gag ccc Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys Asp Val Glu Pro 550 555 560	1737
ggc atc tta cta cat ggg ctg aag ccc tgg act cag tac gcc gtt tac Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln Tyr Ala Val Tyr 565 570 575 580	1785
gtc aag gct gtg acc ctc acc atg gtg gag aac gac cat atc cgt ggg Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp His Ile Arg Gly 585 590 595	1833
gcc aag agt gag atc ttg tac att cgc acc aat gct tca gtt cct tcc Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala Ser Val Pro Ser 600 605 610	1881
att ccc ttg gac gtt ctt tca gca tcg aac tcc tct tct cag tta atc Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser Ser Gln Leu Ile 615 620 625	1929
gtg aag tgg aac cct ccc tct ctg ccc aac ggc aac ctg agt tac tac Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn Leu Ser Tyr Tyr 630 635 640	1977
att gtg cgc tgg cag cgg cag cct cag gac ggc tac ctt tac cgg cac Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr Leu Tyr Arg His 645 650 655 660	2025
aat tac tgc tcc aaa gac aaa atc ccc atc agg aag tat gcc gac ggc Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys Tyr Ala Asp Gly 665 670 675	2073
acc atc gac att gag gag gtc aca gag aac ccc aag act gag gtg tgt Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys Thr Glu Val Cys 680 685 690	2121
ggg ggg gag aaa ggg cct tgc tgc gcc tgc ccc aaa act gaa gcc gag Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys Thr Glu Ala Glu 2169	2169

## 49321-137.ST25.txt

695	700	705	
aag cag gcc gag aag gag gag gct gaa tac cgc aaa gtc ttt gag aat Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys Val Phe Glu Asn 710 715 720			2217
ttc ctg cac aac tcc atc ttc gtg ccc aga cct gaa agg aag cgg aga Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu Arg Lys Arg Arg 725 730 735 740			2265
gat gtc atg caa gtg gcc aac acc acc atg tcc agc cga agc agg aac Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser Arg Ser Arg Asn 745 750 755			2313
acc acg gcc gca gac acc tac aac atc acc gac ccg gaa gag ctg gag Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro Glu Glu Leu Glu 760 765 770			2361
aca gag tac cct ttc ttt gag agc aga gtg gat aac aag gag aga act Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn Lys Glu Arg Thr 775 780 785			2409
gtc att tct aac ctt cgg cct ttc aca ttg tac cgc atc gat atc cac Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg Ile Asp Ile His 790 795 800			2457
agc tgc aac cac gag gct gag aag ctg ggc tgc agc gcc tcc aac ttc Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser Ala Ser Asn Phe 805 810 815 820			2505
gtc ttt gca agg act atg ccc gca gaa gga gca gat gac att cct ggg Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp Asp Ile Pro Gly 825 830 835			2553
cca gtg acc tgg gag cca agg cct gaa aac tcc atc ttt tta aag tgg Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile Phe Leu Lys Trp 840 845 850			2601
ccg gaa cct gag aat ccc aat gga ttg att cta atg tat gaa ata aaa Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met Tyr Glu Ile Lys 855 860 865			2649
tac gga tca caa gtt gag gat cag cga gaa tgt gtg tcc aga cag gaa Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val Ser Arg Gln Glu 870 875 880			2697
tac agg aag tat gga ggg gcc aag cta aac cgg cta aac ccg ggg aac Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu Asn Pro Gly Asn 885 890 895 900			2745
tac aca gcc cgg att cag gcc aca tct ctc tct ggg aat ggg tcg tgg Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly Asn Gly Ser Trp 905 910 915			2793
aca gat cct gtg ttc ttc tat gtc cag gcc aaa aca gga tat gaa aac Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr Gly Tyr Glu Asn 920 925 930			2841
ttc atc cat ctg atc atc gct ctg ccc gtc gct gtc ctg ttg atc gtg			2889

## 49321-137.ST25.txt

Phe Ile His Leu Ile Ile Ala Leu Pro Val Ala Val Leu Leu Ile Val	
935 940 945	
gga ggg ttg gtg att atg ctg tac gtc ttc cat aga aag aga aat aac	2937
Gly Gly Leu Val Ile Met Leu Tyr Val Phe His Arg Lys Arg Asn Asn	
950 955 960	
agc agg ctg ggg aat gga gtg ctg tat gcc tct gtg aac ccg gag tac	2985
Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser Val Asn Pro Glu Tyr	
965 970 975 980	
ttc agc gct gct gat gtg tac gtt cct gat gag tgg gag gtg gct cgg	3033
Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu Trp Glu Val Ala Arg	
985 990 995	
gag aag atc acc atg agc cgg gaa ctt ggg cag ggg tcg ttt ggg	3078
Glu Lys Ile Thr Met Ser Arg Glu Leu Gly Gln Gly Ser Phe Gly	
1000 1005 1010	
atg gtc tat gaa gga gtt gcc aag ggt gtg gtg aaa gat gaa cct	3123
Met Val Tyr Glu Gly Val Ala Lys Gly Val Val Lys Asp Glu Pro	
1015 1020 1025	
gaa acc aga gtg gcc att aaa aca gtg aac gag gcc gca agc atg	3168
Glu Thr Arg Val Ala Ile Lys Thr Val Asn Glu Ala Ala Ser Met	
1030 1035 1040	
cgt gag agg att gag ttt ctc aac gaa gct tct gtg atg aag gag	3213
Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser Val Met Lys Glu	
1045 1050 1055	
ttc aat tgt cac cat gtg gtg cga ttg ctg ggt gtg gtg tcc caa	3258
Phe Asn Cys His His Val Val Arg Leu Leu Gly Val Val Ser Gln	
1060 1065 1070	
ggc cag cca aca ctg gtc atc atg gaa ctg atg aca cgg ggc gat	3303
Gly Gln Pro Thr Leu Val Ile Met Glu Leu Met Thr Arg Gly Asp	
1075 1080 1085	
ctc aaa agt tat ctc cgg tct ctg agg cca gaa atg gag aat aat	3348
Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu Met Glu Asn Asn	
1090 1095 1100	
cca gtc cta gca cct cca agc ctg agc aag atg att cag atg gcc	3393
Pro Val Leu Ala Pro Pro Ser Leu Ser Lys Met Ile Gln Met Ala	
1105 1110 1115	
gga gag att gca gac ggc atg gca tac ctc aac gcc aat aag ttc	3438
Gly Glu Ile Ala Asp Gly Met Ala Tyr Leu Asn Ala Asn Lys Phe	
1120 1125 1130	
gtc cac aga gac ctt gct gcc cgg aat tgc atg gta gcc gaa gat	3483
Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Val Ala Glu Asp	
1135 1140 1145	
ttc aca gtc aaa atc gga gat ttt ggt atg acg cga gat atc tat	3528
Phe Thr Val Lys Ile Gly Asp Phe Gly Met Thr Arg Asp Ile Tyr	
1150 1155 1160	



## 49321-137.ST25.txt

gag aca gac tat	tac cgg aaa gga ggc	aaa ggg ctg ctg ccc	gtg	3573
Glu Thr Asp Tyr	Tyr Arg Lys Gly Gly	Lys Gly Leu Leu Pro	Val	
1165	1170	1175		
cgc tgg atg tct	cct gag tcc ctc	aag gat gga gtc ttc	acc act	3618
Arg Trp Met Ser	Pro Glu Ser Leu	Lys Asp Gly Val Phe	Thr Thr	
1180	1185	1190		
tac tcg gac gtc	tgg tcc ttc ggg	gtc gtc ctc tgg	gag atc gcc	3663
Tyr Ser Asp Val	Trp Ser Phe Gly	Val Val Leu Trp	Glu Ile Ala	
1195	1200	1205		
aca ctg gcc gag	cag ccc tac cag	ggc ttg tcc aac	gag caa gtc	3708
Thr Leu Ala Glu	Gln Pro Tyr Gln	Gly Leu Ser Asn	Glu Gln Val	
1210	1215	1220		
ctt cgc ttc gtc	atg gag ggc ggc	ctt ctg gac aag	cca gac aac	3753
Leu Arg Phe Val	Met Glu Gly Gly	Leu Leu Asp Lys	Pro Asp Asn	
1225	1230	1235		
tgt cct gac atg	ctg ttt gaa ctg	atg cgc atg tgc	tgg cag tat	3798
Cys Pro Asp Met	Leu Phe Glu Leu	Met Arg Met Cys	Trp Gln Tyr	
1240	1245	1250		
aac ccc aag atg	agg cct tcc ttc	ctg gag atc atc	agc agc atc	3843
Asn Pro Lys Met	Arg Pro Ser Phe	Leu Glu Ile Ile	Ser Ser Ile	
1255	1260	1265		
aaa gag gag atg	gag cct ggc ttc	cgg gag gtc tcc	ttc tac tac	3888
Lys Glu Glu Met	Glu Pro Gly Phe	Arg Glu Val Ser	Phe Tyr Tyr	
1270	1275	1280		
agc gag gag aac	aag ctg ccc gag	ccg gag gag ctg	gac ctg gag	3933
Ser Glu Glu Asn	Lys Leu Pro Glu	Pro Glu Glu Leu	Asp Leu Glu	
1285	1290	1295		
cca gag aac atg	gag agc gtc ccc	ctg gag ccc tcg	gcc tcc tcg	3978
Pro Glu Asn Met	Glu Ser Val Pro	Leu Asp Pro Ser	Ala Ser Ser	
1300	1305	1310		
tcc tcc ctg cca	ctg ccc gac aga	cac tca gga cac	aag gcc gag	4023
Ser Ser Leu Pro	Leu Pro Asp Arg	His Ser Gly His	Lys Ala Glu	
1315	1320	1325		
aac ggc ccc ggc	cct ggg gtg ctg	gtc ctc cgc gcc	agc ttc gac	4068
Asn Gly Pro Gly	Pro Gly Val Leu	Val Leu Arg Ala	Ser Phe Asp	
1330	1335	1340		
gag aga cag cct	tac gcc cac atg	aac ggg ggc cgc	aag aac gag	4113
Glu Arg Gln Pro	Tyr Ala His Met	Asn Gly Gly Arg	Lys Asn Glu	
1345	1350	1355		
cgg gcc ttg ccg	ctg ccc cag tct	tcg acc tgc tga	tccttgatc	4159
Arg Ala Leu Pro	Leu Pro Gln Ser	Ser Thr Cys		
1360	1365			
ctgaatctgt gcaaacagta	acgtgtgcgc acgcgcagcg	gggtgggggg ggagagagag		4219
ttttaacaat ccattcacia	gcctcctgta cctcagtga	tcttcagttc tgcccttgct		4279

## 49321-137.ST25.txt

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gcccgcggga gacagcttct ctgcagtaaa acacatttgg gatgttcctt ttttcaatat 4339
gcaagcagct ttttattccc tgcccaaacc cttaactgac atgggccttt aagaacctta 4399
atgacaacac ttaatagcaa cagagcactt gagaaccagt ctcctcactc tgtccctgtc 4459
cttccctggt ctccctttct ctctcctctc tgcttcataa cggaaaaata attgccacaa 4519
gtccagctgg gaagcccttt ttatcagttt gaggaagtgg ctgtccctgt ggccccatcc 4579
aaccactgta cacaccgcc tgacaccgtg ggtcattaca aaaaaacacg tggagatgga 4639
aatttttacc tttatctttc acctttctag ggacatgaaa ttacaaagg gccatcgttc 4699
atccaaggct gttaccattt taacgctgcc taattttgcc aaaatcctga actttctccc 4759
tcacggcccc ggcgctgatt cctcgtgtcc ggaggcatgg gtgagcatgg cagctgggtg 4819
ctccatttga gagacacgct ggcgacacac tccgtccatc cgactgcccc tgctgtgctg 4879
ctcaaggcca caggcacaca ggtctcattg cttctgacta gattattatt tgggggaact 4939
ggacacaata ggtctttctc tcagtgaagg tggggagaag ctgaaccggc 4989

```

<210> 18  
 <211> 1367  
 <212> PRT  
 <213> Homo sapiens

<400> 18

Met Lys Ser Gly Ser Gly Gly Gly Ser Pro Thr Ser Leu Trp Gly Leu  
 1 5 10 15

Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile  
 20 25 30

Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg  
 35 40 45

Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile  
 50 55 60

Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val  
 65 70 75 80

Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu  
 85 90 95

Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe  
 100 105 110

49321-137.ST25.txt

Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile  
 115 120 125

Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu  
 130 135 140

Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile  
 145 150 155 160

Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys  
 165 170 175

Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys  
 180 185 190

Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr  
 195 200 205

Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys  
 210 215 220

Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser  
 225 230 235 240

Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr  
 245 250 255

Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu  
 260 265 270

Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala  
 275 280 285

Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met  
 290 295 300

Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr  
 305 310 315 320

Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys  
 325 330 335

Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly

49321-137.ST25.txt

340

345

350

Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn  
 355 360 365

Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val  
 370 375 380

Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser  
 385 390 395 400

Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly  
 405 410 415

Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp  
 420 425 430

Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe  
 435 440 445

Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu  
 450 455 460

Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg  
 465 470 475 480

Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr  
 485 490 495

Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr  
 500 505 510

Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys  
 515 520 525

Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys  
 530 535 540

Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys  
 545 550 555 560

Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln  
 565 570 575

49321-137.ST25.txt

Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp  
 580 585 590

His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala  
 595 600 605

Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser  
 610 615 620

Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn  
 625 630 635 640

Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr  
 645 650 655

Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys  
 660 665 670

Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys  
 675 680 685

Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys  
 690 695 700

Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys  
 705 710 715 720

Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu  
 725 730 735

Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser  
 740 745 750

Arg Ser Arg Asn Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro  
 755 760 765

Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn  
 770 775 780

Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg  
 785 790 795 800

Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser  
 805 810 815

## 49321-137.ST25.txt

Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp  
820 825 830

Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile  
835 840 845

Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met  
850 855 860

Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val  
865 870 875 880

Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu  
885 890 895

Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly  
900 905 910

Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr  
915 920 925

Gly Tyr Glu Asn Phe Ile His Leu Ile Ile Ala Leu Pro Val Ala Val  
930 935 940

Leu Leu Ile Val Gly Gly Leu Val Ile Met Leu Tyr Val Phe His Arg  
945 950 955 960

Lys Arg Asn Asn Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser Val  
965 970 975

Asn Pro Glu Tyr Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu Trp  
980 985 990

Glu Val Ala Arg Glu Lys Ile Thr Met Ser Arg Glu Leu Gly Gln Gly  
995 1000 1005

Ser Phe Gly Met Val Tyr Glu Gly Val Ala Lys Gly Val Val Lys  
1010 1015 1020

Asp Glu Pro Glu Thr Arg Val Ala Ile Lys Thr Val Asn Glu Ala  
1025 1030 1035

Ala Ser Met Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser Val  
1040 1045 1050

49321-137.ST25.txt

Met Lys Glu Phe Asn Cys His His Val Val Arg Leu Leu Gly Val  
1055 1060 1065

Val Ser Gln Gly Gln Pro Thr Leu Val Ile Met Glu Leu Met Thr  
1070 1075 1080

Arg Gly Asp Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu Met  
1085 1090 1095

Glu Asn Asn Pro Val Leu Ala Pro Pro Ser Leu Ser Lys Met Ile  
1100 1105 1110

Gln Met Ala Gly Glu Ile Ala Asp Gly Met Ala Tyr Leu Asn Ala  
1115 1120 1125

Asn Lys Phe Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Val  
1130 1135 1140

Ala Glu Asp Phe Thr Val Lys Ile Gly Asp Phe Gly Met Thr Arg  
1145 1150 1155

Asp Ile Tyr Glu Thr Asp Tyr Tyr Arg Lys Gly Gly Lys Gly Leu  
1160 1165 1170

Leu Pro Val Arg Trp Met Ser Pro Glu Ser Leu Lys Asp Gly Val  
1175 1180 1185

Phe Thr Thr Tyr Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp  
1190 1195 1200

Glu Ile Ala Thr Leu Ala Glu Gln Pro Tyr Gln Gly Leu Ser Asn  
1205 1210 1215

Glu Gln Val Leu Arg Phe Val Met Glu Gly Gly Leu Leu Asp Lys  
1220 1225 1230

Pro Asp Asn Cys Pro Asp Met Leu Phe Glu Leu Met Arg Met Cys  
1235 1240 1245

Trp Gln Tyr Asn Pro Lys Met Arg Pro Ser Phe Leu Glu Ile Ile  
1250 1255 1260

Ser Ser Ile Lys Glu Glu Met Glu Pro Gly Phe Arg Glu Val Ser

49321-137.ST25.txt

1265

1270

1275

Phe Tyr Tyr Ser Glu Glu Asn Lys Leu Pro Glu Pro Glu Glu Leu  
 1280 1285 1290

Asp Leu Glu Pro Glu Asn Met Glu Ser Val Pro Leu Asp Pro Ser  
 1295 1300 1305

Ala Ser Ser Ser Ser Leu Pro Leu Pro Asp Arg His Ser Gly His  
 1310 1315 1320

Lys Ala Glu Asn Gly Pro Gly Pro Gly Val Leu Val Leu Arg Ala  
 1325 1330 1335

Ser Phe Asp Glu Arg Gln Pro Tyr Ala His Met Asn Gly Gly Arg  
 1340 1345 1350

Lys Asn Glu Arg Ala Leu Pro Leu Pro Gln Ser Ser Thr Cys  
 1355 1360 1365

&lt;210&gt; 19

&lt;211&gt; 22

&lt;212&gt; DNA

&lt;213&gt; artificial sequence

&lt;220&gt;

&lt;223&gt; exon 8 primer (3' PCR amplification primer; see EXAMPLE I)

&lt;400&gt; 19

aacacagcgg tgtgagaagt gc

22

&lt;210&gt; 20

&lt;211&gt; 28

&lt;212&gt; DNA

&lt;213&gt; artificial sequence

&lt;220&gt;

&lt;223&gt; intron 9 primer (5' PCR amplification primer; see EXAMPLE I)

&lt;400&gt; 20

gtatcggtag ttcatttcct ttggttgc

28

&lt;210&gt; 21

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; artificial sequence

&lt;220&gt;

&lt;223&gt; 3' PCR amplification primer for rat intron 8 region



49321-137.ST25.txt

<400> 21  
ctacctgtct acggaagtgg

20

<210> 22  
<211> 20  
<212> DNA  
<213> artificial sequence

<220>  
<223> 5' PCR amplification primer for rat intron 8 region

<400> 22  
ttccgggcag aaatgccagg

20

<210> 23  
<211> 419  
<212> PRT  
<213> Homo sapiens

<400> 23

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu  
1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys  
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His  
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr  
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val  
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu  
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr  
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro  
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser  
130 135 140

## 49321-137.ST25.txt

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln  
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn  
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys  
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser  
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys  
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys  
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu  
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys  
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val  
 340 345 350

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser  
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro  
 370 375 380

49321-137.ST25.txt

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val  
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg  
 405 410 415

Tyr Glu Gly

<210> 24  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<400> 24

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu  
 1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro  
 20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
 50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly  
 65 70 75